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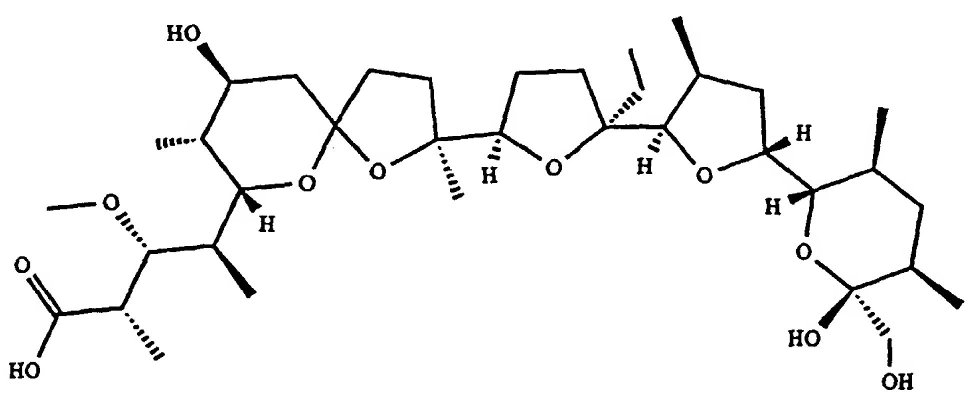
(54) Title: POLYKETIDES AND THEIR SYNTHESIS



monensin A : R = ethyl
monensin B : R = methyl

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(57) Abstract: The complete sequence of the gene cluster for the monensin type I polyketide synthase, from *S. cinnamonensis*, is provided. Thus variant polyketides containing monensin-derived elements can be genetically engineered. Furthermore there are features, e.g. a regulatory protein *mon RI*, which are of wide utility.

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POLYKETIDES AND THEIR SYNTHESIS

The present invention relates to processes and materials (including enzyme systems, nucleic acids, vectors and cultures) for preparing polyketides, particularly polyethers but including polyenes, macrolides and other polyketides by recombinant synthesis, and to the polyketides so produced, particularly novel polyketides. (N.B the term "polyketide" is being used in its conventional sense to include structures notionally derived by the reduction and/or other processing or modification of one or more Ketide units). Furthermore the invention provides the entire nucleic acid sequence of the biosynthetic gene cluster that governs the production of the ionophoric antibiotic polyether polyketide monensin in *Streptomyces cinnamonensis*, and the use of all or part of the cloned DNA first, in the specific detection of other polyether biosynthetic gene clusters; secondly in the engineering of mutant strains of *S. cinnamonensis* and of other actinomycetes which are suitable host strains for the high level production of novel recombinant polyketides; and thirdly in the provision of recombinant biosynthetic genes which lead to such novel polyketide products.

Polyketides are a large and structurally diverse

class of natural products that includes many compounds possessing antibiotic or other pharmacological properties, such as erythromycin, tetracyclines, rapamycin, avermectin, monensin, epothilones and FK506. In particular, polyketides are abundantly produced by *Streptomyces* and related actinomycete bacteria. They are synthesised by the repeated stepwise condensation of acylthioesters in a manner analogous to that of fatty acid biosynthesis. The greater structural diversity found among natural polyketides arises from the selection of (usually) acetate or propionate as "starter" or "extender" units; and from the differing degree of processing of the β-keto group observed after each condensation. Examples of processing steps include reduction to β-hydroxyacyl-, reduction followed by dehydration to 2-enoyl-, and complete reduction to the saturated acylthioester. The stereochemical outcome of these processing steps is also specified for each cycle of chain extension. In addition, the biosynthetic pathways to many polyketides involve additional enzyme-catalysed modifications which may include: methylation by O- and C-methyltransferases, hydroxylation by cytochrome P450 enzymes, other oxidation or reduction processes, and the biosynthesis and attachment of novel sugars and/or deoxy sugars.

The biosynthesis of polyketides is initiated by a group of chain-forming enzymes known as polyketide synthases. Two classes of polyketide synthase (PKS) have been described in actinomycetes. One class, named Type I PKSs, represented by the PKSs for the macrolides erythromycin, oleandomycin, avermectin and rapamycin, consists of a different set or "module" of enzymes for each cycle of polyketide chain extension. (For examples see Cortés, J. *et al.* Nature (1990) 348:176-178; Donadio, S. *et al.* Science (1991) 252:675-679; Swan, D.G. *et al.* Mol. Gen. Genet. (1994) 242:358-362; MacNeil, D.J. *et al.* Gene (1992) 115:119-125; Schwecke, T. *et al.* Proc. Natl. Acad. Sci. USA (1995) 92:7839-7843.)

The term "extension module" as used herein refers to the set of contiguous domains, from a β-ketoacyl-ACP synthase ("KS") domain to the next acyl carrier protein ("ACP") domain, which accomplishes one cycle of polyketide chain extension. The term "loading module" is used to refer to any group of contiguous domains which accomplishes the loading of the starter unit onto the PKS and thus renders it available to the KS domain of the first extension module. The length of polyketide formed has been altered, in the case of erythromycin biosynthesis, by specific relocation using genetic engineering of the enzymatic domain of the erythromycin-

producing PKS that contains the chain releasing thioesterase/cyclase activity (Cortés J. *et al.* Science (1995) 268:1487-1489; Kao, C.M. *et al.* J. Am. Chem. Soc. (1995) 117:9105-9106).

In-frame deletion of the DNA encoding part of the ketoreductase domain in module 5 of the erythromycin-producing PKS (also known as 6-deoxyerythronolide B synthase, DEBS) has been shown to lead to the formation of erythromycin analogues 5,6-dideoxy-3-α-mycarosyl-5-oxoerythronolide B, 5,6-dideoxy-5-oxoerythronolide B and 5,6-dideoxy,6-β-epoxy-5-oxoerythronolide B (Donadio, S. *et al.* Science (1991) 252:675-679). Likewise, alteration of active site residues in the enoylreductase domain of module 4 in DEBS, by genetic engineering of the corresponding PKS-encoding DNA and its introduction into *Saccharopolyspora erythraea*, led to the production of 6,7-anhydroerythromycin C (Donadio, S. *et al.* Proc. Natl. Acad. Sci. USA (1993) 90:7119-7123).

International Patent Application number WO 93/13663 describes additional types of genetic manipulation of the DEBS genes that are capable of producing altered polyketides. However many such attempts are reported to have been unproductive (Hutchinson, C.R. and Fujii, I. Annu. Rev. Microbiol. (1995) 49:201-238, at p. 231). The complete DNA sequence of the genes from *Streptomyces*

hygroscopicus that encode the modular Type I PKS governing the biosynthesis of the macrocyclic immunosuppressant polyketide rapamycin has been disclosed (Schwecke, T. *et al.* (1995) Proc. Natl. Acad. Sci. USA 92:7839-7843). The DNA sequence is deposited in the EMBL/Genbank Database under the accession number X86780.

WO 98/01546 discloses that a PKS gene assembly (particularly of Type I) encodes a loading module which is followed by at least one extension module. The first open reading frame encodes the first multi-enzyme or cassette (DEBS1) which consists of three modules: the loading module (ery-load) and two extension modules (modules 1 and 2). The loading module comprises an acyltransferase and an acyl carrier protein. This may be contrasted with Figure 1 of WO 93/13663 (referred to above). This shows ORF1 as only two modules, the first of which is in fact both the loading module and the first extension module.

WO 98/01546 describes in general terms the production of a hybrid PKS gene assembly comprising a loading module and at least one extension module. It also describes (see also Marsden, A.F.A. *et al.* Science (1998) 279:199-202) construction of a hybrid PKS gene assembly by grafting the wide-specificity loading module for the avermectin-producing polyketide synthase onto the first

multi-enzyme component (DEBS1) for the erythromycin PKS in place of the normal loading module. Certain novel polyketides can be prepared using the hybrid PKS gene assembly, as described for example in WO 98/01571.

WO 98/01546 further describes the construction of a hybrid PKS gene assembly by grafting the loading module for the rapamycin-producing polyketide synthase onto the first multi-enzyme component (DEBS1) for the erythromycin PKS in place of the normal loading module. The loading module of the rapamycin PKS differs from the loading modules of DEBS and the avermectin PKS in that it comprises a CoA ligase domain, an enoylreductase ("ER") domain and an ACP, so that suitable organic acids including the natural starter unit 3,4-dihydroxycyclohexane carboxylic acid may be activated *in situ* on the PKS loading domain and, with or without reduction by the ER domain, transferred to the ACP for intramolecular loading of the KS of extension module 1 (Schwecke, T. *et al.* Proc. Natl. Acad. Sci. USA (1995) 92:7839-7843). WO 98/51695 and WO 98/49315 describe additional types of genetic manipulation of the DEBS genes that are capable of producing altered polyketides.

The second class of PKS, named Type II PKSs, is represented by the synthases for aromatic compounds. Type II PKSs contain only a single set of enzymatic activities

for chain extension and these are re-used as appropriate in successive cycles (Bibb, M.J. *et al.* EMBO J. (1989) 8:2727-2736; Sherman, D.H. *et al.* EMBO J. (1989) 8:2717-2725; Fernandez-Moreno, M.A. *et al.* J. Biol. Chem. (1992) 267:19278-19290). The "extender" units for the Type II PKSs are usually acetate units, and the presence of specific cyclases dictates the preferred pathway for cyclisation of the completed chain into an aromatic product (Hutchinson, C.R. and Fujii, I. Ann. Rev. Microbiol. (1995) 49:201-238). Hybrid polyketides have been obtained by the introduction of cloned Type II PKS gene-containing DNA into another strain containing a different Type II PKS gene cluster, for example by introduction of DNA derived from the gene cluster for actinorhodin, a blue-pigmented polyketide from *Streptomyces coelicolor*, into an anthraquinone polyketide-producing strain of *Streptomyces galileus* (Bartel, P.L. *et al.* J. Bacteriol. (1990) 172:4816-4826).

The minimal number of domains required for polyketide chain extension on a Type II PKS when expressed in a *Streptomyces coelicolor* host cell (the "minimal PKS") has been defined for example in WO 95/08548 as containing the following three polypeptides which are products of the *actI* genes: firstly KS; secondly a polypeptide termed the CLF with end-to-end

amino acid sequence similarity to the KS but in which the essential active site residue of the KS, namely a cysteine residue, is substituted either by a glutamine residue or, in the case of the PKS for a spore pigment such as the *whiE* gene product (Davis, N.K. and Chater, K.F. Mol. Microbiol. (1990) 4:1679-1691) by a glutamic acid residue; and finally an ACP. The CLF has been stated (for example in WO 95/08548) to be a factor that determines the chain length of the polyketide chain that is produced by the minimal PKS. However it has been found (Shen, B. *et al.* J. Am. Chem. Soc. (1995) 117:6811-6821) that when the CLF for the octaketide actinorhodin is used to replace the CLF for the decaketide tetracenomycin in host cells of *Streptomyces glaucescens*, the polyketide product is not found to be altered from a decaketide to an octaketide, so the exact rôle of the CLF remains unclear. An alternative nomenclature has been proposed in which KS is designated KSα and CLF is designated KSβ, to reflect this lack of knowledge (Meurer, G. *et al.* Chemistry & Biology (1997) 4:433-443). The mechanism by which acetate starter units and acetate extender units are loaded onto the Type II PKS is not known, but it is speculated that the malonyl-CoA: ACP acyltransferase of the fatty acid synthase of the host cell can fulfil the same function for the Type II PKS (Revill, W.P. *et al.* J.

Bacteriol. (1995) 177:3946-3952).

WO 95/08548 describes the replacement of actinorhodin PKS genes by heterologous DNA from other Type II PKS gene clusters, to obtain hybrid polyketides. It also describes the construction of a strain of *Streptomyces coelicolor* which substantially lacks the native gene cluster for actinorhodin, and the use in that strain of a plasmid vector pRM5 derived from the low-copy number vector SCP2* isolated from *Streptomyces coelicolor* (Bibb, M.J. and Hopwood, D.A. J. Gen. Microbiol. (1981) 126:427-442) and in which heterologous PKS-encoding DNA may be expressed under the control of the divergent *actI/ actIII* promoter region of the actinorhodin gene cluster (Fernandez-Moreno, M.A. *et al.* J. Biol. Chem. (1992) 267:19278-19290). The plasmid pRM5 also contains DNA from the actinorhodin biosynthetic gene cluster encoding the gene for a specific activator protein, ActII-orf4. The ActII-orf4 protein is required for transcription of the genes placed under the control of the *actI/actIII* bidirectional promoter and activates gene expression during the transition from growth to stationary phase in the vegetative mycelium (Hallam, S.E. *et al.* Gene (1988) 74:305-320).

Type II clusters in *Streptomyces* are known to be activated by pathway-specific activator genes (Narva,

K.E. and Feitelson, J.S. J. Bacteriol. (1990) 172:326-333; Stutzman-Engwall, K.J. *et al.* J. Bacteriol. (1992) 174:144-154; Fernandez-Moreno, M.A. *et al.* Cell (1991) 66:769-780; Takano, E. *et al.* Mol. Microbiol. (1992) 6:2797-2804; Gramajo, H.C. *et al.* Mol. Microbiol. (1993) 7:837-845). The DnrI gene product complements a mutation in the *actII*-orf4 gene of *S. coelicolor*, implying that DnrI and ActII-orf4 proteins act on similar targets. A gene (*srmR*) has been described (EP 0 524 832 A2) that is located near the Type I PKS gene cluster for the macrolide polyketide spiramycin. This gene specifically activates the production of the macrolide antibiotic spiramycin, but no other examples have been found of such a gene. Also, no homologues of the ActII-orf4/DnrI/RedD family of activators have been described that act on Type I PKS genes. WO 98/01546 describes the use of the ActII-orf4 family of activators in conjunction with their cognate promoters (e.g actII-orf4 with the *actI* promoter) in a heterologous actinomycete to obtain high level expression of recombinant Type I polyketide synthase genes.

Although large numbers of therapeutically important polyketides have been identified, there remains a need to obtain novel polyketides that have enhanced properties or possess completely novel bioactivity. The complex

polyketides produced by Type I PKSs are particularly valuable, in that they include compounds with known utility as anthelminthics, insecticides, immunosuppressants, antifungal agents or antibacterial agents. Because of their structural complexity, such novel polyketides are not readily obtainable by total chemical synthesis, nor by chemical modifications of known polyketides.

There is also a need to develop reliable and specific ways of deploying individual genes and portions of genes in practice so that all, or a large fraction, of hybrid PKS genes that are constructed, are viable and produce the desired polyketide product. This includes the development of advantageous host strains for expression of such genes. For example many polyketides are rendered bioactive by the action of further enzymes other than the polyketide synthase, and host strains that contain and are able to express the genes for such enzymes are particularly convenient for the efficient synthesis of the bioactive material. In those cases where the construction of a known or a novel polyketide requires specialised precursors, host strains containing and able to express the genes for key enzymes that enhance the production of such specialised precursors are equally valuable and desirable. There is also a need to develop

rational methods of increasing the expression level of all the genes required for production of a specific polyketide. Clearly also a host cell which is advantageous for the above reasons, and/or because of other favourable characteristics including but not limited to its speed of growth, excellent handling characteristics in fermentation, and ease of transformation with DNA by various techniques, can be made even more favourable by the cloning into that cell of such auxiliary genes for polyketide modification, or gene activation, or post-translational modification, or precursor supply.

The DNA sequences have been disclosed for several Type I PKS gene clusters that govern the production of 16-membered macrolide polyketides, including the tylosin PKS from *Streptomyces fradiae* (application EP 0 791 655 A2), the niddamycin PKS from *Streptomyces caelestis* (Kavakas, S.J. *et al.* J. Bacteriol. (1997) 179:7515-7522) and the spiramycin PKS from *Streptomyces ambofaciens* (application EP 0791 655 A2). DNA sequences have also been disclosed for Type I PKS gene clusters that govern the production of further complex polyketides, for example rifamycin from *Amycolatopsis mediterranei* (WO 98/07868), and soraphen from *Sorangium cellulosum* (US

5716849), but so far no DNA sequence has been disclosed for one of the most widespread and important classes of complex polyketides, the polyethers.

Polyethers form an important group of complex polyketide antibiotics (Westley, J.W. in "Antibiotics IV. Biosynthesis" (Corcoran, J.W. Ed.), Springer-Verlag, New York (1981) p. 41-73). They are polyoxygenated carboxylic acids which act as selective ionophores transporting cations across the cell membrane of target cells and thereby causing depolarisation and cell death. Certain polyethers including monensin, lasalocid and tetronasin are in widespread use in animal husbandry as coccidiostats (principally targetted against *Eimeria spp.*) and as growth promoters. Polyethers have also been reported to be active *in vitro* and *in vivo* against the malarial parasite *Plasmodium falciparum* (Gumila, C. *et al.* Antimicrobial Agents and Chemotherapy (1997) 41: 523-529).

Polyethers contain multiple asymmetric centres and are characterised by the presence of tetrahydrofuran and tetrahydropyran rings, producing a characteristic shape which is non-polar on its outer surface and therefore well adapted for transport of material across bacterial membranes; and provides on its inner surface polar coordinating ligands for a centrally-bound metal ion. In

addition to tetrahydrofuran and tetrahydropyran rings, other groups which are often present include spiroketal, dispiroketal, and substituted benzoic acid moieties and occasionally other groups for example a tetronic acid or a 6-membered carbocyclic ring -

Monensins A and B are produced by the actinomycete *Streptomyces cinnamonensis*. Their structures are shown in Figure 1. Monensin B differs from monensin A only in the presence of a methyl sidechain at C-16 rather than an ethyl sidechain. Monensin selectively binds and transports sodium ions. In addition to its antibacterial and antifungal properties monensin has some activity against protozoal parasites such as the malarial parasite *Plasmodium falciparum*. Although the structures of polyethers differ significantly from those of other complex polyketides such as the polyhydroxylated and polyene macrolides, their biosynthesis appears to take place by a metabolic pathway which has many common elements. Thus experiments using carbon 14-labelled precursors have shown that monensin A is synthesised from five acetate, one butyrate and seven propionate units (Day, L.E. *et al.* Antimicrob. Agents Chemother. (1973) 4:410-414). Similarly experiments using precursors doubly-labelled with carbon-13 and oxygen-18 have shown that oxygens (O)1, (O)3, (O)4, (O)5, (O)6 and (O)10 of

monensin arise from the carboxylate oxygens of either propionate or acetate, while growth in the presence of oxygen-18 oxygen gas demonstrated that the three remaining ether oxygens (O)7, (O)8 and (O)9 are derived from molecular oxygen (Cane, D.E. *et al.*, J. Am. Chem. Soc. (1981) 103:5962-5965; Cane, D.E. *et al.* J. Am. Chem. Soc. (1982) 104:7274 - 7281; Ajaz, A.A. and Robinson, J.A. J. Chem. Soc. Chem. Commun. (1983) 12:679-680). These findings have been rationalised by proposing that the biosynthesis of monensin proceeds via an acyclic triene intermediate (1) in which the geometry of all three carbon-carbon double bonds is E (entgegen) rather than Z (zusammen). The triene is then proposed to be subject to epoxidation to a tri-epoxide (2) and then ring opening is proposed to occur with concomitant sequential formation of the five ether rings as shown in Figure 2A. Such a biosynthetic pathway, first mooted by Westley in 1974 (Westley J.W. *et al.*, J. Antibiot. (1974) 27:597-604) accounts for the observed stereochemistry at the multiple asymmetric centres in monensin, (Cane, D.E. *et al.* J. Am. Chem. Soc. (1982) 104:7274-7281; Sood, G.R. *et al.* J. Chem. Soc. Chem. Commun. (1984) 21:1421-1424) and analogous schemes can be used to account for the biosynthesis of other known polyethers. such as lasalocid A (Hutchinson C.R. *et al.*, J. Am. Chem. Soc. (1981)

103:5953-5956), tetronasin (ICI 139603) (Demetriadou, A.K. *et al.* J. Chem. Soc. Chem. Commun. (1985) 7:408-410) and narasin (Spavold, Z. *et al.* Tetrahedron Letters (1986) 27:3299-3302). The hydroxylation at C-26 and the introduction of an O-methyl group on oxygen 3-are proposed to occur as late steps in the biosynthesis, after formation of the polyether structure.

Unfortunately key aspects of the biosynthetic scheme shown in Figure 2A have so far eluded experimental confirmation. No biosynthetic intermediates have been isolated from mutants of *S. cinnamonensis* that are blocked in early stages of monensin production. 26-deoxymonensin A has been isolated from a *S. cinnamonensis* mutant partially blocked in monensin production (Ashworth, D.M. *et al.* J. Antibiot. (1989) 42:1088-1099) and 3-O-demethylmonensins A and B have been recovered as minor components from the fermentation broth of a monensin-producing strain (Pospisil, S. *et al.* J. Antibiot. (1987) 40:555-557). When fed to cells of *S. cinnamonensis* in radio-labelled form, neither 26-deoxymonensin A, nor 3-O-demethylmonensin A, nor 3-O-demethyl, 26-deoxymonensin A were significantly incorporated into monensin A (Ashworth, D.M. *et al.* J. Antibiot. (1989) 42:1088-1099), either because they are actively excluded or because these modifications in fact

occur earlier in the biosynthetic pathway so that these metabolites are shunt products not readily converted into the final antibiotic by the respective hydroxylase or methyltransferase. Similarly, the putative all (E)-triene precursor (1) has been synthesised and shown not to become incorporated into monensin when fed to growing cells of *S. cinnamonensis* (Holmes, D.S. *et al.* Helv. Chim. Acta (1990) 73:239-259). An alternative pathway has been proposed, as shown in Fig 2B, based on the transition-metal-mediated oxidation of 1,5-dienes (Walba, D.M. and Edwards, P.D. Tetrahedron Lett. (1980) 21:3531-3534). The triene intermediate (4) would different from that of Figure 2A (1) only in that each carbon-carbon double bond would have the (Z)-configuration (Townsend, C.A. and Basak, A. Tetrahedron (1991) 47:2591-2602) and not the (E)- configuration.

The genetic basis of secondary metabolite biosynthesis essentially exists in the genes which code for the individual biosynthetic enzymes and in the regulatory elements which control the expression of the biosynthetic genes. The genes encoding biosynthesis of polyketides in actinomycetes have hitherto been found as clusters of adjacent genes, ranging in size from 20 kilobasepairs (kbp) to over 100 kbp. The clusters often contain specific regulatory genes and genes

conferring resistance of the producing strain to its own antibiotic.

In various of its aspects the invention provides the following:-

(1) a DNA sequence encoding at least one-peptide necessary for the biosynthesis of monensin, preferably comprising one or more of the following genes: *mon BI, mon BII, mon CI, mon CII, mon H, mon RI, mon RII, mon T, mon AIX* and *mon AX* as depicted in the appended sequence data or an allele or mutation thereof;

(2) a DNA sequence according to the first aspect comprising all of the genes listed therein or an allele or mutation thereof;

(3) a DNA sequence according to the first aspect comprising the complete monensin gene cluster;

(4) a DNA sequence coding for one or more of the peptides set out below, said peptide having the amino acid sequence as set out in the appended sequence data or being a variant thereof having the specified activity:

peptide	activity
mon CII	epoxyhydrolase/cyclase
mon E	S-adenosylmethionine-dependent methyltransferase
mon T	monensin resistance gene
mon RII	repressor protein
mon AIX	thioesterase

mon AI	polyketide synthase multienzyme
mon AII	polyketide synthase multienzyme
mon AIII	polyketide synthase multienzyme
mon AIV	polyketide synthase multienzyme
mon AVI	polyketide synthase multienzyme
mon AVII	polyketide synthase multienzyme
mon AVIII	polyketide synthase multienzyme
mon H	regulatory protein
mon CI	flavin-dependent epoxidase
mon BII	carbon-carbon double bond isomerase
mon BI	carbon-carbon double bond isomerase
mon D	cytochrome P450 hydroxylase
mon RI	activator protein
mon AX	thioesterase

(5) a recombinant cloning or expression vector comprising a DNA sequence according to any of aspects 1-4;

(6) a transformant host cell which has been transformed to contain a DNA sequence according to any of aspects 1-4 and is capable of expressing a corresponding peptide;

(7) a hybridization probe comprising a polynucleotide which binds specifically to a region of the monensin gene cluster selected from *mon BI, mon BII, mon CI, mon CII, mon H, mon RI, mon RII, mon T, mon AIX* and *mon AX;*

(8) use of a probe according to aspect (7) in a method of detecting the presence of a gene cluster which governs the synthesis of a polyether, and optionally isolating a gene cluster detected thereby;

(9) Use of a probe comprising a polynucleotide which binds specifically to a gene responsible for levels of activity of the monensin gene cluster, preferably a regulatory gene, resistance gene or thioesterase gene, more preferably the regulatory gene *mon RI*, in a method of detecting an analogous gene in a gene cluster of another polyketide, preferably a polyether, and optionally manipulating the gene detected thereby to alter the level of expression of said other polyketide;

(10) a host cell, preferably *Streptomyces cinnamonensis*, containing a heterologous gene under the control of the *mon RI* gene and a monensin promoter;

(11) use of a portion of the monensin gene cluster having chain terminating activity, preferably comprising at least one of *mon AIX* and *mon AX* or a mutant or allele thereof having chain terminating activity, to effect chain release of a peptide other than one required for monensin biosynthesis;

(12) use of a portion of the monensin gene cluster having carbon-carbon double bond isomerase activity, preferably comprising at least one of *mon BI* and *mon BII*

or a mutant or allele thereof having isomerase activity to provide a desired stereochemical outcome in the synthesis of a polyketide other than monensin;

(13) a polypeptide encoded by a portion of the monensin gene cluster, preferably comprising at least one of *mon BI* and *mon BII* or a mutant or allele thereof, having carbon-carbon double bond isomerase activity;

(14) an epoxidase enzyme encoded by *mon CI* or a derivative or variant thereof having epoxidase activity;

(15) a cyclase enzyme encoded by *mon CII* or a derivative or variant thereof having cyclase activity.

Some embodiments of the invention will now be described by way of example with reference to the accompanying drawings in which:

Fig 1 shows the structure of monensins A and B;

Fig 2 illustrates proposed biosynthetic pathways;

Fig 3 illustrates the proposed organization of the monensin polyketide synthase (PKS) enzyme complex; and

Fig 4 illustrates the proposed organization of the monensin biosynthetic gene cluster.

The overall gene organization of the monensin biosynthetic gene cluster, as shown in Fig 4, is similar to that previously found for many macrolide biosynthetic gene clusters, which have one or more open reading frames (ORFs) encoding large multifunctional PKSs flanked by

other genes which encode functions required for the biosynthesis of the antibiotic. In the case of monensin, there is an unusually high number of distinct ORFs encoding PKS multi-enzymes (eight in total, labelled *monAI* to *monAVIII*) but there is again a separate module of enzymes for each cycle of polyketide chain extension, exactly as found for modular PKSs for macrolide biosynthesis (see Fig 3). Thus there are 12 condensations predicted to be required for the production of the carbon skeleton of monensin, and in agreement with this there are found to be 12 extension modules of PKS enzymes distributed among the 8 PKS ORFs. However, as mentioned in detail below, the other genes in the monensin cluster include genes which have not previously been found in any other gene cluster for the biosynthesis of a complex polyketide, and which are not significantly similar to any genes in published sequence databases. The cloned DNA for these genes is useful to allow the diagnosis that a polyketide biosynthetic gene cluster in any actinomycete, uncovered previously by conventional hybridization against a PKS gene probe from (say) the DEBS or some other characterised PKS gene cluster, is one that governs the synthesis of a polyether; and these genes are also valuable either singly or in combination as specific hybridization probes for the specific detection and

isolation of additional polyether biosynthetic gene clusters. Examples of these previously-unknown genes are the genes *monBI*, *monBII*, *monCI* and *monCII*. In addition the regulatory genes *monH monRI*, and *monRII* and the resistance gene *monT* and the thioesterase genes *monAIX* and *monAX* are all useful for the detection of analogous genes in other polyether clusters which are required for the rational manipulation of such genes in order to increase levels of the specific product.

The cloned and sequenced cluster of genes for *monensin biosynthesis* is useful secondly in the engineering of mutant strains of *S. cinnamonensis* and of other actinomycetes which are suitable strains for the high level production of either natural or novel recombinant polyketides. The sequence of the monensin cluster disclosed here shows the surprising fact, that the gene cluster contains a gene *monRI* whose gene product has an amino acid sequence highly similar to that of *actII*-orf4, the pathway-specific activator gene which activates the *actI* and other promoters of the actinorhodin biosynthetic gene cluster of *Streptomyces coelicolor*. The recognition of this aspect of the natural regulation of a Type I PKS cluster is important and valuable because first, it is possible to increase the yield of monensin by increasing the level of the activator MonRI, either by

placing the gene *monRI* under the control of a powerful promoter or arranging for the presence within the cells of one or more additional copies of the *monRI* gene (as exemplified below); secondly, it will be possible to use the *monRI* gene as a specific hybridisation probe to locate similar genes in other complex PKS gene clusters, especially other polyether PKS gene clusters but also polyene and macrolide gene clusters and all other Type I modular PKS gene clusters; even in cases where (as for rapamycin and erythromycin) no such gene has been previously found within the currently accepted physical limits of the relevant biosynthetic gene cluster. In such cases the *monRI* gene probe might be expected to uncover the activator even if it resides on the chromosome at some distance from the main body of the gene cluster; and simple experiments would then show whether the activator(s) so uncovered are involved in regulation of the biosynthesis of those particular metabolites; thirdly, increasing the copy number of the *monRI* gene or of any of the activator genes uncovered will tend to increase the yield of a heterologous polyketide by "crosstalk" where the activator mimics the presence of the normal activator for the transcription of the genes for that heterologous polyketide synthase. It is clear from recently published work (Wietzorrek, A. and Bibb, M. Mol. Microbiol. (1997)

25:1181-1184) that the ActII-orf4 family of activators exert their effects by binding to promoter regions within the target gene cluster, so it will be possible to use the *monRI* gene together with monensin promoter regions to drive the high-level transcription and translation of heterologous genes in *Streptomyces cinnamonensis*, and perhaps in other host strains too; such genes need not be PKS genes or even involved in polyketide biosynthesis. Monensin promoter regions are found at the 5′ end of genes or groups of genes in the cluster and their location is clear from the sequence analysis disclosed here. Thus a useful vector would provide the monensin promoter and the ribosome binding site and continue up to the start of the open reading frame, after which the monensin ORF naturally found there would be replaced by the heterologous gene. The relative strength of the monensin promoters can be readily determined using any one of a number of known promoter probes, i.e. genes whose expression gives rise to readily measurable and quantifiable effects, such as Green Fluorescent Protein (GFP); or beta-galactosidase in the presence of a chromogenic substrate. It should be possible to mutate randomly the small region of the monensin promoters especially likely to interact with the MonRI activator (identified by the presence of tandem heptanucleotide repeats with a common consensus sequence

between the various monensin promoters) (Wietzorrek, A. and Bibb, M. Mol. Microbiol. (1997) 25:1181-1184), and to determine the optimal DNA sequence for the maximal activation effect using either *S. cinnamonensis* (preferably - in case there are other unknown factors that make the activation function better in this strain than in other heterologous systems), or even in another host actinomycete strain. If the natural monensin promoters were mutated to have this optimal recognition sequence, then this would further increase the production of monensin. By extension, the use of this modified monensin promoter in conjunction with the *monRI* gene in heterologous systems could form the basis of further improvements in expression of polyketide synthases or other genes, either by appropriate chromosomal alterations to introduce the altered promoter and also the *monRI* gene; or by provision of vectors containing these optimised signals linked to specific genes and housed in suitable host cells.

The sequencing of the monensin cluster has uncovered another strategy for gene regulation in such Type I clusters. The previously-sequenced genes for the rapamycin biosynthetic pathway in *Streptomyces hygroscopicus* included a gene of unknown function (*rapH*). A closely similar gene has now been found in the monensin

biosynthetic gene cluster (*monH*), and it is clear from this recurrence (and the comparison of the sequences with those of database proteins) that this gene is potentially an important DNA-binding sensor gene which acts to regulate the transcription of the cluster in concert with other regulatory signals. Simple experimentation is needed in order to define whether the gene is an activator, in which case putting in another copy or increasing its transcription will have the potential to increase polyketide biosynthesis; or alternatively the *rapH* gene product may be a negative regulator, whereupon deletion of this gene may release the biosynthetic pathway from this inhibitory effect and increase yields.

There is a continuing need to develop new methods of high-level production of bioactive metabolites and other valuable gene products in actinomycetes. *Streptomyces cinnamonensis* is a recognised and very valuable industrial strain for the production of very high levels of monensin, it is readily transformable with DNA by standard methods of conjugation or of protoplast transformation, it is a host for numerous known broad range plasmids including well-known expression plasmids of both high- and low-copy number, it also grows quickly relative to other actinomycete strains (for example about three times faster than wild type *Saccharopolyspora erythraea* the

erythromycin producer, under comparable conditions) and sporulates relatively easily. Heterologous polyketides can be expressed in *Streptomyces cinnamonensis* using for example the low-copy number plasmid pCJR24 (which has no origin of replication active in actinomycetes so is maintained by integration into the chromosome) (Rowe, C. *et al.* Gene (1998) 216:215-223) or the related plasmid pCJR29 in which the polyketide synthase gene(s) are placed under the control of the *actI* promoter which is activated by the ActII-orf4 activator; or alternatively the *monAI* promoter can be substituted together with the MonRI activator; or some other pairing of activator and cognate promoter chosen from either a Type II or a Type I polyketide synthase gene cluster. As an example, the wild type strain of *Streptomyces cinnamonensis* has been used to express the plasmid pCJR29 (Rowe, C. *et al.* Gene (1998) 216:215-223) containing as insert the three ORFs for the PKS governing the production of 6-deoxyerythronolide B, the macrolide precursor of erythromycin A in *Saccharopolyspora erythraea*, these genes being placed under the control of the pathway-specific *actI* promoter from *Streptomyces coelicolor* together with its cognate activator gene *actII*-orf4. The transformed strain when cultivated in a suitable liquid medium produced 6-deoxyerythronolide B in good yield.

It is well known to the person skilled in the art that it is possible to use standard vectors unable to replicate in actinomycetes to introduce DNA into a *Streptomyces* cell, such DNA comprising two portions of contiguous DNA which are each identical to one of two portions of the cell's chromosome that are spaced up to 100 kbp apart; and that through recombination between the incoming DNA and the chromosome occurring in both portions of DNA the net result is that the chromosomal sequence is replaced by the defective sequence originally that of the incoming DNA. Such a procedure has been applied to the monensin-producing strain of *S. cinnamonensis* as described in detail below, and a strain of *S. cinnamonensis* has been obtained that carries a specific deletion in the monensin cluster and which is unable to produce the antibiotic. The use of such a strain facilitates the production of heterologous polyketides by removal of the background of monensin production.

The multiple uses of portions of the cloned and sequenced DNA from the monensin cluster will readily occur to the person skilled in the art. A surprising feature of the PKS of the monensin cluster is an unusual mechanism of polyketide chain initiation. We have found that the monensin PKS loading module has three domains, which from the amino-terminus of the protein are: a KSq domain, an

acyltransferase domain and an ACP domain. We have uncovered this organisation in the PKS for the 14-membered macrolide oleandomycin as well as in the monensin PKS, an organisation of the loading module previously only found for the 16-membered macrolides and in which the KSq domain (which looks like a ketosynthase or condensation domain except that the active site cysteine residue is substituted by a glutamine for which the single letter notation is Q) had been previously speculated to have no function. It was realised that the acyltransferase of the loading module actually has malonyl-CoA and not acetyl-CoA as a substrate and that KSq is an active decarboxylase. It appears that a better discrimination can be achieved in the selection of the smaller acetate unit over propionate if the choice is made initially between methylmalonyl- and malonyl-CoA.

An unprecedented feature of the monensin PKS genes is that no integral chain-terminating domain is present as a C-terminal appendage of the PKS extension module that catalyzes the twelfth and final chain extension. Because the product of the monensin PKS is a carboxylic acid, it would have been firmly predicted that chain release would have been catalyzed by such a C-terminal domain containing a "thioesterase" activity. Previously sequenced PKS gene sets have been of two sorts: first, those macrolide PKSs

typified by erythromycin, spiramycin, tylosin, niddamycin which have a readily recognisable C-terminal "thioesterase" domain, which in these enzymes functions as a specific cyclase rather than releasing the polyketide product as a free carboxylic acid; secondly, those macrolide PKSs typified by rapamycin, FK506, and rifamycin, where there is an alternative and recognised mode of chain termination by transfer of the polyketide chain to an acceptor moiety, catalyzed by a specific enzyme (eg pipecolate incorporating enzyme for rapamycin (Schwecke T. *et al.* Proc. Natl. Acad. Sci. USA (1995) 92:7839-7843) and FK506 (Mothamedi H. and Shafiee A, Eur. J. Biochemistry (1998) 256:528-534); arylamine synthetase for rifamycin (August P.R. *et al.* Chemistry & Biology (1998) 5:69-79).

The monensin PKS surprisingly falls into neither category, and therefore seems to be the first example of a novel mode of chain termination. It is novel and noteworthy in this connection that the monensin PKS gene cluster contains two small genes that encode discrete, monofunctional thioesterase enzymes. Although many PKS gene clusters have been previously shown to contain one such discrete thioesterase, none have been shown to have two. The role of such thioesterases is not known, although in the case of methymycin/pikromycin PKS, which has been

reported to be responsible for the biosynthesis of both the 12-membered macrolide methymycin and the 14-membered macrolide pikromycin (Xue Y.Q. Proc. Natl. Acad. Sci. USA (1998) 95:12111-12116) the disruption of this thioesterase reportedly caused a ten-fold drop in the amount of both macrolides produced. A similar finding has been reported for the discrete thioesterase of the tylosin PKS gene cluster (Cundliffe E. *et al.* Chemistry & Biology in press). Additional copies of such thioesterases may therefore accelerate the production of specific polyketide, but this has not yet been demonstrated. However, the presence of the discrete thioesterase is not completely essential for polyketide production.

It is highly desirable to have a broadly effective method of catalysing the release of polyketide gene products from a PKS as the free acid. The well-studied integral thioesterase domain in the erythromycin PKS thioesterase has a broad specificity in cyclization to form a lactone (assuming that a hydroxy group is present in the growing polyketide chain at an appropriate position), but hydrolysis to form the free acid is very slow. The recognition of the unusual arrangement of the monensin PKS means that it is now possible to harness either the entire PKS module that catalyses the twelfth and final extension cycle in monensin biosynthesis, or the

C-terminal portion of it, and graft it onto a different polyketide synthase by genetic engineering, so as to allow the release mechanism characteristic of monensin to operate in a different context. The use of this portion only of the monensin PKS suffices to allow the novel mechanism of chain release to operate successfully. The speed of the polyketide chain hydrolysis in a given case can depend on the additional presence of one or both of the discrete thioesterase genes (*monAIX* and *monAX*) from the monensin gene cluster. The use of this novel method of chain termination represents a valuable way of generating a large number of novel engineered polyketides that are currently inaccessible, and ensuring that the products have a specified chain length.

The genes *monBI* and *monBII* appear to encode very similar enzymes with significant amino acid sequence similarity to authentic ketosteroid isomerases which are known to catalyse the migration of an activated carbon-carbon double bond. The conservation of active site residues makes it very likely that these *mon* genes govern a reaction involving activated double bonds in the biosynthetic pathway to monensin and this surprising observation can be accommodated if the initial product of the polyketide chain growth on the monensin PKS is a linear precursor in which the double bonds were initially

formed with a conventional *trans* or E (entgegen) geometry; but before the polyketide chain was extended by insertion of the next unit the *monBI* and/or the *monBII* gene product(s) catalyse the specific rearrangement of the newly-created double bond into the *cis* or Z (zusammen) geometry. This new view of the monensin biosynthetic pathway allows the deduction that the *monBI* and *monBII* genes, perhaps in combination with specific portions of the monensin modules where they normally exert their effects (namely modules 3, 5 and 7) might be used in order to achieve the extremely desirable targetted biosynthesis of novel polyketides containing double bonds with Z geometry at specified point(s) along the chain. Thus for example it should be possible to provide for the direct biosynthesis of C22-C23 *cis* or Z double bond in avermectins, thus avoiding tedious and expensive chemical conversion of an initial fermentation product into this important anthelminthic. Only limited experimentation is needed to see whether the *monBI* and/or *monBII* gene products are sufficient or whether the *mon* PKS at modules 3, 5 and 7 forms part of the specific docking site(s) for the isomerases and therefore must also be used in the creation of the hybrid PKS that will insert the *cis* or Z double bond at the desired position. The substrate specificity of the isomerases need not be limited to 2,3-

unsaturated thioesters. The purified enzymes could also be used to effect such isomerisations *in vitro*, depending on the position of the equilibrium or whether further enzymes are used to achieve the further transformation of the product as it is formed (*vide infra*).

The product of the *monCI* gene is a novel oxidative enzyme with some sequence similarity to authentic examples of such enzymes in the databases; and with a clearly definable role in the monensin biosynthetic pathway, the epoxidation of the double bonds at three separate positions in the initially-formed acyclic intermediate in monensin biosynthesis. This epoxidase could therefore be used in conjunction with *monBI/monBII* gene products to effect oxidative reactions on suitable substrates *in vitro* and *in vivo*. Similarly the *monCII* gene product is a putative cyclase that opens the epoxides and causes the formation of ether rings in monensin.

Any or all of the *monBI, monBII, monCI or monCII* genes may be introduced into a heterologous strain containing the gene cluster for another polyether, in order to divert the biosynthetic pathway and produce a polyketide of altered structure. In these experiments the analogues of these *monB* genes could either be present or (once located and characterised using the *mon* genes as probes) they may be deleted prior to the introduction of

the *monB* and *monC* genes into that strain. The converse experiment in which analogues of the *monB* and *monC* genes from other strains are introduced into *S. cinnamonensis* likewise has the potential to produce novel oxidised polyketides. Also, the *monB* and *monC* genes or their analogues may be introduced into a strain that normally produces a macrolide or a polyene or some other complex polyketide and expressed there, when they may effect the diversion of the growing polyketide chain on a heterologous modular PKS towards a new product, which may or may not have the structure of a polyether.

The availability of the monensin gene sequence allows the institution of domain swaps to alter the acyltransferase (AT) specificity of a given module, for example the ethylmalonyl-CoA specific extender found in one of the modules of the monensin PKS can be used to replace one of the other ATs to generate an ethyl side branch at that position in the chain, or the AT can be used to substitute in any other (e.g. macrolide) PKS, as described in WO 98/01571 and WO 98/01546. Similarly the alteration of the level of reduction in a module, by manipulation of the reductive enzymes, can be applied to the monensin genes and here it will produce, depending on which module is affected, either an altered monensin, or a

species which is only partly cyclised, or a polyether with an altered pattern of cyclisation, or even a linear polyketide.

In general the targetted alteration of the pattern of substitution of sidechains or reduction level along the polyketide chain produced by the monensin PKS will, like the disruption or deletion of the oxidative enzymes mentioned above, lead to non-polyether polyketide products. It should be possible, by introduction of the DEBS thioesterase at the C-terminus of one of the later modules of the monensin PKS, together with an appropriately placed hydroxy group earlier in the chain, to produce novel macrolide products from this polyether PKS system, or alternatively novel polyenes of defined chain length and chosen ring size.

Example 1

Cloning of the monensin A biosynthetic gene cluster using DNA probes derived from the erythromycin-producing polyketide synthase of *Saccharopolyspora erythraea*

A genomic library of the monensin A producing strain *Streptomyces cinnamonensis* ATCC 15413 was constructed using methods well-known in the art, namely, the production of high molecular weight genomic DNA, followed by the partial cleavage of this DNA using the frequent-cutting restriction enzyme *Sau*3A, fractionation of the fragments on a sucrose gradient and selection of fragments of average size 35-40 kbp, and the cloning of these fragments into the cosmid vector pWE15 (Evans, G.A. *et al.* Gene (1989) 79:9-20) which had been previously digested with *Bam*HI and treated with shrimp alkaline phosphatase. The library was packaged and transfected into *Escherichia coli* XL-1 Blue MR cells. The library was plated out on 2xTY agar medium (10 g tryptone, 10 g yeast extract, 5 g NaCl, 15 g bactoagar per litre containing ampicillin 50 μg/ml) for cosmid selection and the colonies were allowed to grow overnight. The library was then screened by hybridisation using as a probe DNA encoding the ketosynthase domain of module 1 of the erythromycin-producing PKS (6-deoxyerythronolide B synthase, DEBS) of *Saccharopolyspora erythraea*. The colonies giving a

positive hybridisation signal in the hybridisation were selected and the cosmid DNA from each colony was purified and mapped by restriction digestion. The presence of the target biosynthetic genes on a cosmid was verified by sequencing of the ends of the cosmid inserts using the commercially available T3 and T7 primers which hybridise specifically to the respective ends of each cosmid insert (Evans, G.A. *et al.* Gene (1989) 79:9-20).

Example 2

Sequencing of the biosynthetic gene cluster for monensin A from *Streptomyces cinnamonensis*

Three cosmids obtained by screening of the genomic library of *S. cinnamonensis* were used to obtain the entire DNA sequence of the monensin biosynthetic gene cluster. These cosmids, MO.CN02, MO.CN11 and MO.CN33 between them contain the entire DNA sequence of the cluster and the adjacent regions of the chromosome. They have been deposited in NCIMB, 23 St Machair Drive, Aberdeen AB24 3RY, UK, under the NCIMB accession numbers 40956 (MO-CN11); 40957 (MO-CN33) and 40958 (MO-CN02) respectively.

The DNA of each cosmid was separately subjected to partial digestion with *Sau*3A and fragments of approximately 1.5-2.0 kbp were separated by agarose gel electrophoresis. The fragments were then ligated into the

plasmid vector pUC18 (Messing, 1982), previously digested with *BamHI* and treated with shrimp alkaline phosphatase. The library was transformed into *E. coli* strain XL1-Blue MR and plated on 2xTY agar medium containing ampicillin (100 µg/ml) to select for plasmid-containing cells. Plasmid DNA was purified from individual colonies and sequenced using the Sanger dye-terminator procedure on an ABI 377 automated sequencer (Sanger, F. Science (1981) 214:1205-1210). The sequence data obtained from single random subclones of a cosmid was assembled into a single continuous sequence and edited using GAP4.1 program of the STADEN gene analysis package (Staden, R. Molecular Biotechnology (1996) 5:233-241).

The sequence is set out in the appended sequence listing.

Tables I and II contain data about individual genes and gene products.

Example 3

Inactivation of the monensin A biosynthetic gene cluster

A chromosomal gene disruption experiment was used to verify the identity of the cloned polyketide synthase gene cluster. Plasmid pMOB6314 is a pUC18 sequencing subclone of the presumed monensin A biosynthetic gene cluster prepared as described in Example 1, whose inserted DNA comprises the DNA sequence from nucleotide 9763 to

nucleotide 10108 in SEQ ID 1, and which therefore contains a region of DNA wholly internal to *orfE*, a putative 3-O-methyltransferase. A *Hin*dIII fragment containing the thiostrepton resistance gene *tsr* from plasmid pIJ702 (Katz, E. *et al*. J. Gen. Microbiol. (1983) 129:2703-2714) was cloned into the *Hin*dIII site of plasmid pMOB6314 and the ligation mixture was used to transform *E. coli* cells. Transformants bearing the required plasmid pMOΔE01 were identified by isolation of plasmid DNA and analysis by restriction digestion. pMOΔE01. Plasmid pMOΔE01 was used to transform protoplasts of *Streptomyces cinnamonensis* as described by (Hopwood D.A. *et al*. (1985)). Since plasmid pMOΔE01 lacks an origin of replication that is active in *Streptomyces*, growth in the presence of thiostrepton (25 μg/ml) in the regeneration medium led to the isolation of stable integrants. Isolated putative integrants were tested for the presence of integrated pMOΔE01 sequences by Southern hybridisation. A clone of *Streptomyces cinnamonensis* identified by its restriction pattern in Southern hybridisation as bearing pMOΔE01 integrated in the region of *monE* of the monensin A biosynthetic gene cluster was designated *S. cinnamonensis* MO-DD01.

Detection of production of the monensin A related metabolites produced by *S. cinnamonensis* MO-DD01 was performed by GC-MS analysis of methanol extracts of the

entire broth harvested in 72 hours of growth of the strain. No significant amounts of monensin A-related metabolite production were detectable.

Example 4

Overproduction of erythromycin aglycone in *Streptomyces cinnamonensis*

S. cinnamonensis is a suitable system for overproduction not just of monensin A but also of other polyketide metabolites. Established techniques of genetic transformation allow fast introduction of foreign polyketide producing genes sets into this host. Fast growth of *S. cinnamonensis* in liquid culture and optimal precursor supply favour high yield of polyketide metabolites.

Construction of pIB061

S. erythraea NRRL2338 was transformed with pCJR30 (Rowe, C. J., et al. (1998) Gene 216:215-223) using a routine protoplast transformation technique as described by Hopwood et al. (1985). A stable integrant of *S. erythraea* [pCJR30] was identified and the production of 10mg/L of the triketide lactone (delta lactone of (2S,3R,4R,5R)-2,4-dimethyl-3,5-dihydroxy-heptanoic acid) in addition to erythromycins was confirmed by MS analysis.

Total DNA of *S. erythraea* [pCJR30] was purified and

approximately 200 ng was digested with *Eco*RI endonuclease. The digestion mixture was precipitated with isopropanol and the resulting DNA was treated with T4 DNA-ligase for 16 hours at 16°C. The ligation mixture was used to transform *E.coli* DH10B cells. The transformants were screened for the presence of the plasmid. A clone containing a 44.7kb plasmid was identified and confirmed by restriction analysis to contain three complete genes: *ery*AI, *ery*AII and *ery*AIII. The plasmid was named pIB061.

Transformation of *S. cinnamonensis*

Protoplasts of *S. cinnamonensis* were prepared by a modified procedure of Hopwood *et al.* (1985). Plasmid pIB061 was transformed into the protoplasts of *S. cinnamonensis* and stable thiostrepton resistant colonies were isolated. Individual colonies were checked for their plasmid content and the presence of plasmid pIB061 was confirmed by its restriction pattern. *S. cinnamonensis* (pIB061) was inoculated into 250 ml of M-C3 minimal production medium containing 10 μg/ml of thiostrepton and allowed to grow for 72 hours at 30 °C. After this time the mycelia were removed by filtering. The broth was extracted with two volumes of ethyl acetate and the combined ethyl acetate extracts were washed with an equal volume of saturated sodium chloride, dried over anhydrous sodium sulphate, and the ethyl acetate was removed under reduced

pressure to give about 200 mg of crude product. The product was analysed by LCQ and mass was confirmed to that of erythronolide B.

This example demonstrates the importance of *S. cinnamonensis* for production of high levels of foreign polyketide antibiotics. Introduction of the complete erythromycin gene cluster or other gene clusters into this system are likely to produce high levels of the corresponding metabolites.

Example 5

Construction of plasmid pCJW58 containing the monensin activator gene under the ermE* promoter

The ermE* promoter derived from the *ermE* resistance methyltransferase gene of *S. erythraea* (Bibb *et al.* Gene (1985) 38:215-226) was amplified by PCR as a *Spe*I-*Xba*I fragment using the following oligonucleotides 5'-CCACTAGTATGCATGCGAGTGTCCGTTCGAGT-3' and 5'-TTGTATACACCTAGGATGGTTGGCCGTGC-3' with pRH3 (Dhillon *et al.* Molecular Microbiology (1989) 3:1405-1414 as a template and cloned into *Sma*I-digested, phosphatase-treated pUC18, to produce plasmid pIB135. The integrative plasmid pSET152 (Bierman, M. *et al.* (1992) Gene 116:43-49)) was digested with *Xba*I and the backbone was dephosphorylated and ligated to the *Spe*I-*Xba*I fragment of pIB135 containing the *ermE** promoter. The ligation mixture was used to

transform *E. coli* DH10B and the orientation of the insert in the plasmids from individual clones was checked by using restriction analysis. A plasmid with the *erm*E* promoter oriented so that the *Nde*I and *Xba*I sites are adjacent to the apramycin resistance gene was selected and named pIB139.

The *monR* gene from the monensin biosynthetic gene cluster was amplified and *Nde*I and *Xba*I restriction sites introduced at 5′ and 3′ ends respectively, by PCR using as primers the following oligonucleotides:
5′-AGA TAC CAT ATG CTG GGC CCG CTC CGC AT -3′
and 5′-AAT GCT CTA GAC TGT CAG CGA CCG GAC AGG GCC AA-3′
and cosmid MO.CN11 as template. The PCR product was ligated into *Sma*I-treated and phosphatase-treated plasmid pUC18 and the ligation mixture was used to transform *E. coli* DH10B cells. Transformant colonies were analysed for the presence of plasmid and the identity of the plasmid inserts was verified by sequencing. A plasmid whose insert contained the *monR* gene flanked by *Nde*I and *Xba*I restriction sites was selected and designated pCJW57.

Plasmid pCJW57 was digested with *Nde*I and *Xba*I and the fragment containing the monR gene was ligated together with the backbone of plasmid pIB139 which had been digested with the same two restriction enzymes, and purified by gel elution. The ligation mixture was used to

transform *E. coli* strain DH10B cells. Transformant colonies were analysed for the presence of plasmid and the identity of the plasmid inserts was verified by restriction analysis. One such recombinant was selected and named plasmid pCJW58.

Plasmid pCJW58 was used to transform the methylation-deficient *E. coli* strain ET 12567 (MacNeil D. J. et al. (1992) Gene 111:61-68) and the recovered, unmethylated plasmid was then used to transform the same *E. coli* strain ET12567 housing the plasmid pUB307, a derivative of RP4 which is *mob*⁻ and which contains a gene for kanamycin resistance (Piffaretti, J. C. et al. (1988) Mol. Gen. Genet. 212:215-218). Recombinants were plated on 2 x TY agar medium containing apramycin and kanamycin at final concentrations of 50 micrograms per ml and 50 micrograms per ml respectively. The plasmid content of recombinants was checked isolation of plasmid DNA and checking of the identity of these plasmids by restriction analysis. One such clone which contained both pUB307 and plasmid pCJW58 was selected and used for further experiments.

Construction of *Streptomyces cinnamonensis* (pCJW58) and production of monensins

A single colony of *E. coli* ET12567 housing both pUB307 and pCJW58 was toothpicked into 3 ml of TY liquid medium, containing apramycin and kanamycin at 25 and 25

micrograms respectively, and grown overnight at 37°C. This culture was used to inoculate 25 ml of TY medium, supplemented with the same antibiotics at the same concentrations, and growth was continued until the absorbance at 600 nm (1 cm pathlength) was between 0.3-0.6. The cells were centrifuged (room temperature, 7 minutes, 2000 x *g*), resuspended in TY liquid medium (10 ml) containing no added antibiotics, re-centrifuged as before, then resuspended in 2ml of TSB medium and placed on ice. Meanwhile, 0.5 ml of TSB medium was added to 100 microL containing approximately 10^8 spores of *S. cinnamonensis*. After a brief heat shock, at 50°C for 10 minutes, the suspension was briefly cooled, mixed with 0.5 ml of donor *E. coli* cells, and plated on solid A medium, which has composition as follows:

<u>A medium</u>

Sigma wheat starch	5g
Corn steep powder	1.25g
Yeast extract	1.5g
$CaCO_3$	1.5g
$FeSO_4$	6 mg
DIFCO agar	10g
H_2O	to 500 ml

pH adjusted to pH 7 with KOH.

And to which in addition was added 10 mM $MgCl_2$ to a final concentration of 10 mM.

The plates were allowed to dry overnight at room temperature, and were then allowed to incubate a further 18 hours at 30°C. After this time each 25 ml plate was overlaid with a solution of apramycin (final concentration 50 micrograms per ml) and nalidixic acid (final concentration 20 micrograms per ml), and the plates were allowed to incubate for four days at 30°C. At this time individual colonies were toothpicked onto solid A medium and allowed to grow. Four representative colonies from the A medium plate were grown up in liquid modified YEME medium, which has composition as follows:

<u>Modified YEME medium</u>

Sucrose	100g
DIFCO Yeast extract	3g
Bacto peptone	5g
Oxoid Malt extract	3g
Glucose	10g

H_2O to 1L

pH adjusted to pH 7.2 with NaOH.

These cultures were used to provide a 2% vol/vol inoculum for 30 ml of modified YEME which was grown for 7 days, and then transferred to SM16 medium, which has

composition as follows:

<u>SM16 medium</u>

3-[N-Morpholino]-propane sulfonic acid (MOPS) buffer	20.9g
L-proline	10.0g
Glucose	20g
NaCl	0.5g
K_2HPO_4	2.1g
Ethylenediaminetetraacetic acid, sodium salt	0.25g
$MgSO_4.7H_2O$	0.49g
$CaCl_2.2H_2O$	0.029g
Trace elements solution (Hopwood, D. A. et al. (1985) Genetic Manipulation of *Streptomyces* - a Laboratory Manual, at p.235)	2 ml
0.5 M $CoCl_2$ solution	2 microlitres
H_20 to 1L	

pH adjusted to pH 7 with NaOH.

After growth for a further 7 days, mycelium was collected by centrifugation at 2000 x g for 30 minutes, and the supernatant was extracted three times with 300 ml of ethyl acetate. The combined extracts were concentrated by evaporation under reduced pressure to an oil, which was

mixed with 1 ml of methanol. Samples were applied to an LCQ liquid chromatograph fitted with a mass spectrometer detector unit. The column used was a C18 reversed phase column, equilibrated with a mixture of 80% 20mM ammonium acetate/20% acetonitrile, and the column was eluted with a gradient of increasing acetonitrile, reaching 100% acetonitrile over 24 minutes. Monensins A and B emerged from the column with retention times respectively of 8.2 minutes and 9.2 minutes. The relative amounts of monensin produced by three independent clones (A-C) containing an additional copy of the *monR* gene were compared to a control fermentation of the wild type *S. cinnamonensis* strain, with the results shown in the Table below:

<u>Table showing increased monensin production in strains bearing additional copy of *monR* gene</u>

Strain	monensin A concentration (arbitrary units)	monensin B concentration (arbitrary units)
Control	188	861
A	430	1 800
B	450	1 300
C	249	1 300

<u>Example 6</u>

<u>Construction of *S. cinnamonensis* M12AT5</u>

A region lying immediately 5' of the DNA encoding the

acyltransferase (AT12) domain of module 12 of the monensin polyketide synthase in the monensin biosynthetic gene cluster was amplified with the following primers: 5'-GGTGGCCACGGAAACACCAACACCGGACCCGCGCC-3', and 5'-CTCTCGGAGGCCCGGCGCAACGGCCACAA-3', 3' using cosmid MO-CN11 as a template. The PCR product was ligated into *Sma*I digested and phosphatase-treated plasmid pUC18 and the ligation mixture was used to transform *E. coli* DH10B cells. Transformant colonies were analysed for the presence of plasmid and the identity of the plasmid inserts was verified by sequencing. A plasmid whose insert contained a fragment upstream of the AT12-encoding sequence from about 82.3kb to 83.2kb of the *mon* cluster was designated pMO81. Similarly a region lying immediately 3' of the DNA encoding the acyltransferase (AT12) domain of module 12 of the monensin polyketide synthase in the monensin biosynthetic gene cluster was amplified with the following primers: 5'-GGCCTAGGGCTGCCTCGGGTGGTGGATCTGCCGA-3' and 5'- TGGTCGGGCGCGGTGCGTGCGATACGT-3', using cosmid MO-CN11 as a template. The PCR product was ligated into *Sma*I-treated and dephosphorylated pUC18 and the ligation mixture was used to transform DH10B *E.coli* cells. Transformant colonies were analysed for the presence of plasmid and the identity of the plasmid inserts was verified by sequencing. A plasmid whose insert contained

a fragment downstream of the AT12-encoding sequence, from 80.5kb to 81.4kb of the *mon* cluster, was designated pMO82.

The DNA encoding AT of module 5 was amplified and *Msc*I and *Avr*II restriction enzyme recognition sites were introduced at the ends by PCR using the following primers: 5'-CCTGGCCAGGGCGGCCAGTGGGTGGGCATG-3' and 5'-GGCCTAGGGGTCGGCCGGGAACCAGCGCCGCCAGT-3' and the cosmid MO-CN33 as a template. The PCR product was ligated into *Sma*I-treated and dephosphorylated pUC18 and the ligation mixture was used to transform DH10B *E.coli* cells. Transformant colonies were analysed for the presence of plasmid and the identity of the plasmid inserts was verified by sequencing. A plasmid whose insert DNA, with sequence from about 44.2kb to 45.2kb of the *mon* cluster, encoded the AT5 domain was designated pMO83.

pMO81 was digested with *Msc*I and *Hin*dIII and ligated to the 0.9kb *Msc*I - *Hin*dIII fragment of pMO82. A clone containing both fragments was designated pMO84. Plasmid pMO84 was cleaved with *Avr*II and *Hin*dIII, treated with phosphatase, and ligated together with the 1.0 kb *Avr*II - *Hin*dIII fragment of pMO83 to produce pMO85, which contains the DNA encoding the AT5 domain flanked by DNA from either side of the DNA encoding the AT12 domain of the monensin PKS. The thiostrepton resistance gene *tsr*, derived from plasmid pIJ702 (Katz, E. et al., J. Gen. Microbiol.

1983), was cloned into the *Hin*dIII site of pMO85. The resulting plasmid pMO86 was analysed by its restriction pattern and confirmed to contain all the desired elements.

Plasmid pMO86 was used to transform *S. cinnamonensis* protoplasts as described by Hopwood, D. A. (1985). Stable thiostrepton-resistant transformants were isolated and checked for the desired integration of the pMO85 into the AT12 flanking regions by Southern blot hybridisation. One such integrant, *S. cinnamonensis* MO-08, containing pMO85 integrated upstream of the AT12, was passed through 4 cycles of sporulation on a non-selective nutrient medium. Spores obtained after the fourth cycle were replica-plated onto media with and without thiostrepton. DNA of clones that had lost thiostrepton resistance was analysed by Southern blot hybridisation. Clones in which the DNA encoding the AT12 domain had been replace by the DNA encoding the AT5 domain was designated *S. cinnamonensis* M12-AT5. At this time individual colonies were toothpicked onto solid A medium and allowed to grow. Four representative colonies from the A medium plate were grown up in liquid modified YEME medium, which has composition as follows:

<u>Modified YEME medium</u>

Sucrose	100g
DIFCO Yeast extract	3g
Bacto peptone	5g
Oxoid Malt extract	3g
Glucose	10g
H_2O to 1L	

pH adjusted to pH 7.2 with NaOH.

These cultures were used to provide a 2% vol/vol inoculum for 30 ml of modified YEME which was grown for 7 days, and then transferred to SM16 medium, which has composition as follows:

SM16 medium

3-[N-Morpholino]-propane sulfonic acid (MOPS) buffer	20.9g
L-proline	10.0g
Glucose	20g
NaCl	0.5g
K_2HPO_4	2.1g
Ethylenediaminetetraacetic acid, sodium salt	0.25g
$MgSO_4.7H_2O$	0.49g
$CaCl_2.2H_2O$	0.029g
Trace elements solution (Hopwood, D. A. et al. (1985) Genetic	

Manipulation of *Streptomyces* - a Laboratory Manual, at p.235)	2 ml
0.5 M $CoCl_2$ solution	2 microlitres
H_2O to 1L	

pH adjusted to pH 7 with NaOH.

After growth for a further 7 days, mycelium was collected by centrifugation at 2000 x g for 30 minutes, and the supernatant was extracted three times with 300 ml of ethyl acetate. To confirm presence of the C-2-ethyl substituents of both monensin A and B the combined extracts were concentrated by evaporation under reduced pressure to an oil, which was mixed with 1 ml of methanol. Samples were applied to an LCQ liquid chromatograph fitted with a mass spectrometer detector unit. The column used was a C18 reversed phase column, equilibrated with a mixture of 80% 20mM ammonium acetate/20% acetonitrile, and the column was eluted with a gradient of increasing acetonitrile, reaching 100% acetonitrile over 24 minutes. Mass ions 14 mass units above those expected for both monensin A and B confirmed production of the respective C-2-ethyl substituents.

<u>Example 7. Construction of pSGK005 and its use in the production of C-13 propyl-erythromycin</u>

Plasmid pSGK005 is a pCJR24 based plasmid containing a PKS gene comprising a loading module plus the first and

second extension modules and the chain terminating thioesterase of the PKS responsible for the production of erythromycin (DEBS). The loading module comprises the KS and ethyl-malonyl CoA specific AT from module 5 of the monensin PKS linked to the DEBS loading ACP domain. In addition, the active site cysteine of this module 5 KS has been mutated to glutamine to convert an extender di-domain to a loading di-domain. Plasmid pSGK005 was constructed as follows.

A 2769bp DNA segment of the monensin cluster of *S. cinnamonensis* extending from nucleotide 42438 to 45207 was amplified by PCR using the following oligonucleotide primers. 5'-GTGACGTCATATGTCGAGTGCTGAAGAGTCG-3' and 5'-GGGGTCGCCTAGGAACCAGCGCCGCCAGTCGA-3'

The design of these primers introduced *Nde* I and *Avr* II sites at the ends of the amplifed fragment. Monensin cosmid 05 was used as a template for the reaction. The resulting 2769bp fragment was digested with *Nde* I and *Xho* I and a 656bp fragment (Fragment A) purified by preparative gel electrophoresis.

A second PCR reaction was used with the same template to amplify DNA from nucleotide 43098 to 45207. The primers used were 5'-CGGCCTCGAGGGCCCGTCGGTCAGTGTCGACACGGCGCAGTCCTCCTCGC-3' and 5'-GGGGTCGCCTAGGAACCAGCGCCGCCAGTCGA-3'

The design of the upstream oligonucleotide primer incorporated a change of the codon specifying the KS active site cysteine (nucleotides 43135-43137, TGC) to glutamine (CAG). The resulting 2109bp DNA fragment (Fragment B) was digested with *Xho* I and *Avr* II and purified by preparative gel electrophoresis.

Plasmid pCJW80 is derived from pCJR24 and DEBS1-TE in which *Msc* I and *Avr* II sites have been introduced to flank the AT of the DEBS loading module. This plasmid was digested with *Nde* I and *Avr* II and the larger fragment (Fragment C) purified by preparative gel electrophoresis.

The three fragments (Fragments A, B, C) were ligated together using T4 DNA ligase and the ligation mixture used to transform electrocompetent *E. coli* DH10B cells. Individual clones were checked for the presence of the desired plasmid pSGK005. The identity of pSGK005 was confirmed by restriction pattern and sequence analysis.

Plasmid pSGK005 was used to transform *S. erythraea* NRRL2338 using a routine protoplast transformation technique. Thiostrepton resistant colonies were selected on R2T20 media containing g/ml thiostrepton. Further analysis confirmed that pSGK005 had integrated into the *S. erythraea* NRRL2338 chromosome by Southern blot hybridisation of their genomic DNA with DIG-labelled DNA containing the *act*II *orf4* promoter. The culture *S.*

erythraea NRRL2338 (pSGK005) was inoculated into 5ml tap water medium in a 30ml flask. After three days incubation at 29°C this flask was used to inoculate 30ml of Ery-P medium in a 300ml flask. The broth was incubated at 29°C at 200rpm for 6 days. After this time the whole broth was adjusted to pH8.5 with NaOH, and then extracted twice with an equal volume of ethyl acetate. The ethyl acetate extract was evaporated to dryness at 45°C under a nitrogen stream using a Zymark Turbovap LV evaporator. The product identities were confirmed by LC/MS. A peak was observed with a m/z value of 734 $(M+H)^+$ required for erythromycin A. A second peak was observed with a m/z value of 748 $(M+H)^+$, required for 13-propyl erythromycin A.

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TABLE I

gene	function	start	end
gdhA	glutamate dehydrogenase (partial)	1038	0
dapA	dihydrodipicolinate synthase	2140	1220
orf3	putative transcriptional activator	2211	3152
orf4	hypothetical protein	3264	3680
orf5	hypothetical protein	4307	3684
orf6	hypothetical protein	4570	4758
orf7	hypothetical protein	5058	5612
acpX	acyl carrier protein	6010	5693
ksX	ketoacyl synthase	8531	6045
monCI	probable epoxihydrolase/cyclase	9542	8643
monE	methyltransferase	10426	9596
monT	monensin resistance gene (ABC-	10656	12191
monRI	probable repressor	12205	12780
monAI	*thioesterase*	13829	13023
monAI	polyketide synthase loading &	14121	23198
	KS-L	14172	15486
	AT-L malonate specific	15777	16880
	ACP-L	17019	17276
	KS1	17358	18626
	AT1 methylmalonate specific	18960	19976
	DH1 (potential)	20019	20519
	KR1 (inactive)	21636	22241
	ACP1	22536	22793
monAI	polyketide synthase module 2	23205	29921
	KS2	23307	24569
	AT2 methylmalonate specific	24891	25913
	DH2	25953	26369
	ER2	27600	28463
	KR2	28485	29042
	ACP2	29313	29570
monAI	polyketide synthase modules 3 & 4	29974	42372
	KS3	30076	31347
	AT3 malonate specific	31798	32838
	DH3	32884	33465
	KR3	34692	35181
	ACP3	35553	35811
	KS4	35899	37170
	AT4 methylmalonate specific	37489	38511
	DH4	38557	38982
	ER4	40123	40986
	KR4	41005	41562
	ACP4	41848	42105
monAI	polyketide synthase modules 5 & 6	42448	54564
	KS5	42628	43890
	AT5 ethylmalonate specific	44221	45243
	DH5	45289	45744
	KR5	46785	47337
	ACP5	47593	47850

	KS6	47947	49218
	AT6 malonate specific	49579	50601
	DH6	50644	51075
	ER6	52222	53102
	KR6	53101	53661
	ACP6	54052	54306
monA	polyketide synthase modules 7 & 8	54614	66934
	KS7	54716	55978
	AT7 methylmalonate specific	56300	57319
	DH7	57358	57802
	KR7	59048	59608
	ACP7	59867	60124
	KS8	60185	61453
	AT8 malonate specific	61808	62839
	DH8	62882	63316
	ER8	64577	65437
	KR8	65456	66016
	ACP8	66404	66661
monA	polyketide synthase module 9	66952	72054
	KS9	67075	68340
	AT9 malonate specific	68698	69729
	KR9 (potential)	70735	71262
	ACP9	71536	71783
monH	probable regulator	72051	74993
monCI	FAD containing epoxidase	76541	75051
monBI	double bond isomerase	76960	76538
monBI	double bond isomerase	77450	77016
monA	polyketide synthase modules 11 &	88708	77447
	KS11	88612	87344
	AT11 methylmalonate specific	87022	85993
	KR11	85111	84562
	ACP11	84292	84035
	KS12	83962	82694
	AT12 methylmalonate specific	82354	81335
	DH12 (potential) delta	81286	80855
	ER12 (potential)	79618	78914
	KR12	78895	78337
	ACP12	78070	77812
monA	polyketide synthase module 10	93741	88816
	KS10	93636	92368
	AT10 methylmalonate specific	92040	91021
	KR10	90132	89584
	ACP10	89322	89068
monD	P450 oxygenase	94081	95273
monRI	probable activator	96141	95338
monA	thioesterase	96941	96138
orf29	cell wall biosynthesis capK	97580	98953
lipB	lipase B	99983	98991
orf31	ion pump	101433	100507
orf32	membrane structural protein	102581	101490
amtA	glycine amidinotransferase	102924	103450

TABLE II

GdhA, glutamate dehydrogenase (partial coding sequence) Length: 346 amino acids

```
  1 LTTRPDTKTA LSQKTALSQL LTEIEHRNPA QPEFHQAARE VLETLAPVIA
 51 ARPEYAEAGL IERLCEPERQ IVFRVPWQDD HGRVRVNRGF RVEFNSALGP
101 YKGGLRFHPS VNLGVIKFLG FEQIFKNALT GLGIGGGKGG SDFDPRGRSD
151 AEVMRFCQSF MTELYRHIGE HTDVPAGDIG VGGREIGYLF GQYRRITNRW
201 EAGVLTGKGR NWGGSLIRPE ATGYGNVLFA AAMLRERGET LEGRTAVVSG
251 SGNVAIYTIQ KLAALGANAV TCSDSSGYVV DEKGIDLDLL KQVKEVERAR
301 VDTYAQRRGA SARFVPGRRV WEVPADIALP SATQNELDAD DATALI
```

DapA, dihydrodopicolinate synthase Length: 307 amino acids

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  1 MTLASSLEPT TEPLFNGLYV PLVTPFTDDL RLAPEALARL ADEALSAGAS
 51 GLVALGTTAE AATLTAEERE TVIRVCSAAC RAHGAPLIVG VGTNDTATAI
101 TALRELAARG DVAAALVPAP PYIRPGEAGT LAHFAALAEH GGLPLVVYDI
151 PYRTGQTLGA GTITALGRLP EVVGIKHATG SIDPTTMELL DSPLPGFAVL
201 GGDDIVLSPL VAAGAHGGIV ASANLRTADY AEMIALWRRG SAAPARALGA
251 DLARLSAALF TEPNPTVIKG VLHAQNRIPS PAVRMPLLAA SADSVRRAAP
301 LAASRK*
```

ORF3, putative transcriptional activator protein Length: 314 amino acids

```
  1 MLDVRRLHLL RELDRRGTIA AVAEALTFTA SAVSQQLGVL EREAGVPLLE
 51 RSGRRVVLTP AGRSLVAHAD AVLNRLEQAV AELAGARDGI GGPLRIGTFP
101 SGGHTIVPGA LAELASRHPA LEPMVREIDS ARVSDGLRAG ELDVALVHDY
151 DFVPATPDTT VDEVPLLEEP MYLVTHAADT ATDSGSGSTL AALLGPCAEV
201 PWITARDGTT GHAMAVRACQ AAGFQPRIRH QVNDFRTVLA LVAAGQGAGF
251 VPRMAAEPSP AGVVLTKLPL FRRSKVAFRA GGGAHPAIAA FVAAATTAVE
```

301 RMAGSRGPAG GSE*

ORF4, hypothetical protein Length: 139 amino acids

1 MADDAYLFLL PDRHPRLGAA LAAVGALECT ETPAVHAWLQ AHEASVSSEQ
51 VRILPADAET LIPKDAERLP VPLSEEEALK VEQECAPQTV TDMESELLAF
101 RETTQDWQAL VHRALTAGIP AQRIARLTGL DPEEIGRL*

ORF5, hypothetical protein Length: 208 amino acids

1 LAVAACAAVV LPIDAVVRIS AADVGVLVFF AYLLPYLAIT MTVFVSVAPE
51 QVRSWARREA RGTFLQRYVL GTAPGPGGSL FIAAAALVVA VLWLPGHLST
101 TFSALPRTLV ALALVVAAWI CVVVAFAVTF QADNLVENER ALEFPGERSP
151 AWADYVYFAL AAMTTFGTTD VDVTSRDMRR TVAANTVIAF VFNTVTVAIL
201 VSALGGR*

ORF6, hypothetical protein Length: 63 amino acids

1 MTVMDKLKQM LKGHEDKAGQ GIDKAGDFVD GKTQGKYSGQ VDTAQDKLRD
51 QFGSDQQEPP QR*

ORF7, hypothetical protein Length: 185 amino acids

1 MGTAQSQEQA AAPGACAAFV RFVLCGGGVG LASSFAVVAL ASWVPWALAN
51 ALVAVVSTVV ATELHARFTF GAGGRATWRQ HAQSAGSAAA AYAVTCVAMF
101 VLQQLVAAPG AVLEQVVYLS ASALAGVARF VVLRLVVFAR NRSLPAAAAV
151 RTARPVRRVP APVPATVAHA ASRPAGPAAL CPAA*

AcpX, acyl carrier protein (ACP) Length: 106 amino acids

1 MTSTDHTSGQ DATELEKQLA AATPEEREKL LTDTIRTQAG TLLNTTLSDD
51 SNFLENGLNS LTALELTKTL MTLTGMEIAM VAIVENPTPA QLAHHLGQEL
101 AHTTA*

KsX, ketoacyl-ACP synthase Length: 829 amino acids

1 VANEEKLVEY LKWTTAELHQ AQQQLRELKA AQHEPIAVVS MACRLPGKTR
51 TPDDLWDLVS EGRDAVTGFP DDRAWELPEE RPYAELGGFL DDAAGFDAGF
101 FDISDTEAVA TEPLQRLMLH LAWETVERGH IAPHTLRSTL TGVYVGATGH
151 DYATRLETAP DELLPYLGGG TSGSLVSGRI AYALGLEGPA ISVDTACSSS
201 LVALHLACQA LRRGECGLAL AGGGTVMSTP HTFHAFAHQK SLAQDGRCKP
251 FAAAADGMGL GEGVGLVLLE RLGDARKNGH PVLAVIRGSA VNQDGAGYGL
301 AAPNGPSQQH VIRAALADAG LTPDQIDAVE AHGTGTPIGD AIEVQALLAT
351 YGADRSPDRP LWLGSVKSNT GHTQGAAGAA ALIKMVQAFR HGTLPPTLHV
401 DRPTPLAAWK KGAVRLLTEA VDWPRREEPR RVGISAFATS GTNAHLILEE
451 PPVDEAPVPD AARDQTSPVA PELPVAWSLS ARTPEALRAQ AKALVTHLAA
501 TDPAPSPAEV AYSLAATRSP LEHRAVLTGT DHTELLAAAR ALAAGEDHPD
551 LVRSTPGAGP KKIAWHFDGR PADGVTTGAA PGAKPGATFG ATFGAAFGGA
601 EFHSAFPLFA SAFDEARALL DTHLPTPLPT PHSELARFAV HTALARLLLE
651 TGVRPHTLTG DGVGHIAAAY AAGILTLDDA CRLAAAHAAA AQAAEGEQPA
701 PPDAYEPVLK QLTFQRATLT LTSTAPADTP IASADYWHHH LTSPAPTAPP
751 TPETHTLLHL GALSPEGTQT SAVSALLTAL ARLHTTGGTV DWTPLVRRTP
801 HPRTIDLPTY SFQATRYWLH DHTAHAAV*

MonCII, probable epoxyhydrolase/cyclase Length: 300 amino acids

1 VKNLRIPVSQ TVSLNVRYRP ADGPGAPGRP FLLLHGMLSN ARMWDEVAAR
51 LAAAGHPAYA VDHRGHGESD TPPDGYDNAT VVTDLVAAVT ALDLSGALVA
101 GHSWGAHLAL RLAAEHPDLV AGLALIDGGW YEFDGPVMRA FWERTADVVR
151 RAQQGTTSAA DMRAYLRATH PDWSPTSIEA RLADYRVGPD GLLIPRLTST
201 QVMSIVAGLQ REAPADWYPK VTVPVRLLPL IPAIPQLSDQ VRAWVAAAEA

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251 ALEQVSVRWY PGSDHDLHAG APDEIAADLL LLARSCEAMP GGKAGVRPA*

MonE, S-adeonosylmethionine-dependent methyltransferase Length: 277 amino acids

1 VNKTVAPEPS DIGHYYDHKV FDLMTQLGDG NLHYGYWFDG GEQQATFDEA
51 MVQMTDEMIR RLDPAPGDRV LDIGCGNGTP AMQLARARDV EVVGISVSAR
101 QVERGNRRAR EAGLADRVRF EQVDAMNLPF DDGSFDHCWA LESMLHMPDK
151 QQVLTEAHRV VKPGARMPIA DMVYLNPDPS RPRTATVSDT TIYAALTDIG
201 DYPDIFRAAG WTVLELTDIT RETAKTYDGY VEWIRAHRDE YVDIIGVEGY
251 ELFLHNQAAL GKMPELGYIF ATAQRP*

MonT, putative monensin resistance gene (ABC-transporter) Length: 512 amino acids

1 MSADLGARRW WAVGALVLAS MVVGFDVTIL SLALPAMADD LGANNVELQW
51 FVTSYTLVFA AGMIPAGMLG DRFGRKKVLL TALVIFGIAS LACAYATSSG
101 TFIGARAVLG LGAALIMPTT LSLLPVMFSD EERPKAIGAV AGAAMLAYPL
151 GPILGGYLLN HFWWGSVFLI NVPVVILAFL AVSAWLPESK AKEAKPFDIG
201 GLVFSSVGLA ALTYGVIQGG EKGWTDVTTL VPCIGGLLAL VLFVMWEKRV
251 ADPLVDLSLF RSARFTSGTM LGTVINFTMF GVLFTMPQYY QAVLGTDAMG
301 SGFRLLPMVG GLLVGVTVAN KVAKALGPKT AVGIGFALLA AALFYGATTD
351 VSSGTGLAAA WTAAYGLGLG IALPTAMDAA LGALSEDSAG VGSGVNQSIR
401 TLGGSFGAAI LGSILNSGYR GKLDLDGVPE QAHGAVKDSV FGGLAVARAI
451 KSNGLADSVR SAYVHALDVV LVVSGGLGLL GVVLAVVWLP RHVGQSTAKT
501 AESEHEAADA V*

MonRII, probable repressor protein Length: 192 amino acids

1 VPGLRERKKA RTKAAIQREA VRLFREQGYT ATTIEQIAEA AEVAPSTVFR
51 YFATKQDLVF SHDYDLPFAM MVQAQSPDLT PIQAERQAIR SMLQDISEQE

101 LALQRERFVL ILSEPELWGA SLGNIGQTMQ IMSEQVAKRA GRDPRDPAVR

151 AYTGAVFGVM LQVSMDWAND PDMDFATTLD EALHYLEDLR P*

MonAIX, *thioesterase* Length: 269 amino acids

1 MDRGTAARAP QIGDEFGAAT GNGVWLRRYH AAAEAPVRLV CFPFAGGSAS

51 YYFGLSGLLA PGVEVLAVQY PGRQDRHAEP CLASVAELAD GVVPHLPCDG

101 KPFALFGHSL GAIVAFEVAR RLRGPAGPGL PVHLFVSGGL ARPYRPAGRS

151 GAFGDADILA HLRAMGGTDE RFFRSPELQE LVLPALRADY RAVATYEAPG

201 PGRLDCPITA LIGDADERTS PEQAATWRER TGAAFDLRVL PGGHFYLDGC

251 QEQVAAVVTE ALTAGPGV*

MonAI, polyketide synthase multi-enzyme MONS1, housing loading module and extension module 1 Length: 3026 amino acids

1 MAASASASPS GPSAGPDPIA VVGMACRLPG APDPDAFWRL LSEGRSAVST

51 APPERRRADS GLHGPGGYLD RIDGFDADFF HISPREAVAM DPQQRLLLEL

101 SWEALEDAGI RPPTLARSRT GVFVGAFWDD YTDVLNLRAP GAVTRHTMTG

151 VHRSILANRI SYAYHLAGPS LTVDTAQSSS LVAVHLACES IRSGDSDIAF

201 AGGVNLICSP RTTELAAARF GGLSAAGRCH TFDARADGFV RGEGGGLVVL

251 KPLAAARRDG DTVYCVIRGS AVNSDGTTDG ITLPSGQAQQ DVVRLACRRA

301 RITPDQVQYV ELHGTGTPVG DPIEAAALGA ALGQDAARAV PLAVGSAKTN

351 VGHLEAAAGI VGLLKTALSI HHRRLAPSLN FTTPNPAIPL ADLGLTVQQD

401 LADWPRPEQP LIAGVSSFGM GGTNGHVVVA AAPDSVAVPE PVGVPERVEV

451 PEPVVVSEPV VVPTPWPVSA HSASALRAQA GRLRTHLAAH RPTPDAARVG

501 HALATTRAPL AHRAVLLGGD TAELLGSLDA LAEGAETASI VRGEAYTEGR

551 TAFLFSGQGA QRLGMGRELY AVFPVFADAL DEAFAALDVH LDRPLREIVL

601 GETDSGGNVS GENVIGEGAD HQALLDQTAY TQPALFAIET SLYRLAASFG

651 LKPDYVLGHS VGEIAAAHVA GVLSLPDASA LVATRGRLMQ AVRAPGAMAA
701 WQATADEAAE QLAGHERHVT VAAVNGPDSV VVSGDRATVD ELTAAWRGRG
751 RKAHHLKVSH AFHSPHMDPI LDELRAVAAG LTFHEPVIPV VSNVTGELVT
801 ATATGSGAGQ ADPEYWARHA REPVRFLSGV RGLCERGVTT FVELGPDAPL
851 SAMARDCFPA PADRSRPRPA AIATCRRGRD EVATFLRSLA QAYVRGADVD
901 FTRAYGATAT RRFPLPTYPF QRERHWPAAA GVGQQPETPE LPESSESSEQ
951 AGHEREEGAR AWGGPEGRLA GLSVNDQERV LLGLVTKHVA VVLGDASGTV
1001 QAARTFKQLG FDSMAAAELS ERLGTETGLP LPATLTFDYP TPLAVAAHLR
1051 AELTGTPAPA GSAPATGALG AGDLGTDEDP VAIVAMSCRY PGGAGTPEDL
1101 WRLVADGADA IGDFPTDRGW DLARLFHPDP DRSGTSCTRQ GGFLYDAADF
1151 DAEFFDISPR EALAVDPQQR LLLECAWEAF ERAGLDPRAL KGSPTGVFVG
1201 MTGQDYGPRL HEPSQATDGY LLTGSTPSVA SGRLSFSFGL EGPALTVDTA
1251 CSSSLVTLHL AAQALRRGEC DLALAGGATV LATPGMFTEF SRQRGLAPDG
1301 RCKPFAAGAD GTGWAEGVGL VLLERLSEAR RKGHAVLAVI RGSAINQDGA
1351 SNGLTAPNGP SQQRVIRAAL AAARLTADEV DVVEAHGTGT TLGDPIEAQA
1401 LLATYGQGRS AERPLWLGSV KSNIGHTQAA AGVAGVIKMV MAMRHDLLPA
1451 TLHVDEPSGH VDWSTGAVRL LTEPVVWPRG ERPRRAAVSS FGISGTNAHL
1501 VLEEAGQDEY VAGAADDAGP VDGAVLPWVV SGRTGAALRE QARRLRELVT
1551 GGSADVSVSG VGRSLVTTRA VFEHRAVVVG RDRDTLIGGL EALAAGDASP
1601 DVVCGVAGDV GPGPVLVFPG QGSQWVGMGA QLLGESAVFA ARIDACEQAL
1651 SPYVDWSLTE VLRGDGRELS RVDVVQPVLW AVMVSLAAVW ADHGVTPAAV
1701 VGHSQGEIAA VVVAGALTLE DGAKIVALRS RALRQLSGGG AMASLGVGQE
1751 QAAELVEGHP GVGIAAVNGP SSTVISGPPE QVAAVVADAE ARELRGRVID
1801 VDYASHSPQV DAITDELTHT LSGVRPTTAP VAFYSAVTGT RIDTAGLDTD

1851 YWVTNLRRPV RFADAVTALL ADGHRVFIEA SSHPVLTLGL QETFEEAGVD
1901 AVTVPTLRRE DGGRARLARS LAQAFGAGCA VRWENWFPAT GTSTVELPTY
1951 AFQRRRYWLE APTGTQDAAG LGLAAAGHPL LGAATEIADG DIRLLTGRIS
2001 RHSHPWLAQH TLFGAAVVPA SVLAEWALRA ADEAGCPRVD DLTLRTPLVL
2051 PETAGVQVQI VVGPADARDG HRDFHVYARP DGKDASEGEG IAEGEGASEG
2101 EGASGGTDAP WTCHADGRLV AEPTGTASED SPDTVWPPPG AEPVDLGDFY
2151 ERAAATGVGY GPVFTGLRAL WRRDGELFAE AVLPQEAPET AGFGMHPALL
2201 DAALHPALLG ERPAEEDKVW LPFTLTGVTL WATGATSVRV RLTPLDDDPD
2251 ASADGRAWRV GVSDPTGAEV LTCEALVAVA AGRRELRAAG ERVSDLYAVE
2301 WVPVPGPGPV GEGADFSGWA GLGECGERWE CVGRVERWYE DLDALGAAVE
2351 GGASVPSVVL ATAAAAPGGA GDGAADALSA VRWTGALLDQ WLADARFADA
2401 RLVVITSGAV ATGDDFLPDP AAAAVRGLVE QAQVRHPGRI LLVDTEAGAG
2451 LGVGAGVDDA LLEQAVAMAL GADEPQLALR AGRVLAPRLT APQDAAVTEA
2501 ARPLDPDGTV LITGPAGAPV ADLAEHLVRT GQCRHLLLLP GDGELEEMAE
2551 ELRGLGATVD LSTADPADPT ALAEVVAAVE GDHPLTGVIH ATGVVDAFDP
2601 GDSASDLMID SASDSFAEAW SSRAGVTAAL HTATAHLPLD LFAVLSPAGA
2651 DLGIARSAAA AGADAFSAAL ALRRHTTVTT DTTAPPRTTA PPRTTASPRT
2701 TALSSSRTTG VALAYGPPTA PRPGIKGTAP GRIPVLLDAA RAHGGGSPLL
2751 GARLAARALA AESAAEGVAG LPAPLRALAV AAAAAGAPTR RTAADRKPPA
2801 DWPARLAPLS APEQLRLLID AVRTHAAAVL GRTDPEALRG DATFKQLGLD
2851 SLTAVELRNR LVEDTGLRLP TALVFRYPTP AAIAAHLRER LTSPSETTAT
2901 QRSGGQTPAA GQASSALAPG GSAAGPPAAD TVLSDLTRME NTLSVLAAQL
2951 PHTETGEITT RLEALLTRWK TTNATANDSG DGNGGDDDAA ERLKAASADQ
3001 IFDFIDNELG VGHGTSRVTP TPKAG*

MonAII, polyketide synthase multi-enzyme MONS2, housing extension module 2 Length: 2239 amino acids

1 MASEEQLVEY LRRVTTELHD TRRRLVQEED RRQEPVALVG MACRFPGGVA

51 SPEDLWDLVA AGKDAIEDFP TDRGWDLEAL YDPDPAAYGT SYVRHGGFVD

101 DAGSFDADFF GISPREALAM DPQQRLMLET SWELFERAGI EPVSLKGSRT

151 GVYAGVSSED YMSQLPRIPE GFEGHATTGS LTSVISGRVA YNYGLEGPAV

201 TVDTACSASL VAIHLASQAL RQRECDLALA GGVLVLSSPL MFTEFCRQRG

251 LAPDGRCKPF AAAADGTGFS EGIGLLLLER LSDARRNGHK VLAVIRGSAV

301 NQDGASNGLT APNDAAQEQV IRAALDNARL TPSEVDAVEA HGTGTKLGDP

351 IEAGALLATY GQHRARPLLL GSLKSNIGHT HATAGVAGVI KTVMAIRNGL

401 LPATLHVEEL SPHVDWDAGA VEVVTEPTPW PETGHPRRAG VSAFGISGTN

451 AHLILEEAPP EEDVPAPVVV ESGGVVPWVV SGRTPEALRE QARRLGEFVA

501 GDTDALPNEV GWSLATTRSV FEHRAVVVGR DRDALTAGLG ALAAGEASAG

551 VVAGVAGDVG PGPVLVFPGQ GAQWVGMGAQ LLDESAVFAA RIAECERALS

601 AHVDWSLSAV LRGDGSELSR VEVVQPVLWA VMVSLAAVWA DYGVTPAAVI

651 GHSQGEMAAA CVAGALSLED AARIVAVRSD ALRQLQGHGD MASLSTGAEQ

701 AAELIGDRPG VVVAAVNGPS STVISGPPEH VAAVVADAEA RGLRARVIDV

751 GYASHGPQID QLHDLLTERL ADIRPTNTDV AFYSTVTAER LTDTTALDTD

801 YWVTNLRQPV RFADTIEALL ADGYRLFIEA SAHPVLGLGM EETIEQADMP

851 ATVVPTLRRD HGDTTQLTRA AAHAFTAGAD VDWRRWFPAD PAPRTIDLPT

901 YAFQRRRYWL ADTVKRDSGW DPAGSGHAQL PTAVALADGG VVLNGRVSAE

951 RGGWLGGHVV AGTVLVPGAA LVEWVLRAGD EAGCPSLEEL TLQAPLVLPE

1001 SGGLQVQVVV GAADEQGGRR DVHVYSRSEQ DASAVWQCHA VGELGRASVA

1051 RPVRQAGQWP PAGAEPVEVG GFYEGVAAAG YEYGPAFRGL RAMWRHGDDL

1101 LAEVELPEEA GSPAGFGIHP ALLDAALHPL LAQRSRDGAG AGAHGGQVLL
1151 PFSWSGVSLW ASEATTVRVR LTGLGGGDDE TVSLTVTDPA GGPVVDVAEL
1201 RLRSTSARQV RGSAGPGADG LYELRWTPLP EPLPVPAPAN GRDVAADLSG
1251 CAVLGELVAE PGPGIDLEGC PCYPGVGALA DNASPPSMIL APVHSDTTGG
1301 DGLALTERVL RVIQDFLAAP SLEQKQTRLA FVTRGAADTG STTGGSAAPA
1351 EAVDPAVAAV WGLVRSAQSE NPGRFVLLDT DAPLDQASVA PLVDAVRSAV
1401 EADEPQVALR GGRLLVPRWA RAGEPVELAG PAGARAWRLV GGDSGTLEAV
1451 VAEACDDIVL RPLAPGQVRV AVHTAGVNFR DVLIALGMYP DPDALPGTEA
1501 AGVVTEVGPG VTRLSVGDRV MGMMDGAFGP WAVADARMLA PVPPGWGTRQ
1551 AAAAPAAFLT AWYGLVELAG LKAGERVLIH AATGGVGMAA VQIARHVGAE
1601 VFATASPGKH AVLEEMGIDA AHRASSRDLA FEDAFRQATD GRGVDVVLNS
1651 LTGELLDASL RLLGDGGRFV EMGKSDPRDP ELVALEHPGV SYEAFDLVAD
1701 AGPERLGLML DRLGELFAGG SLVPLPVTAW PLGRAREALR HMSQARHTGK
1751 LVLDVPAPLD PDGTVLVTGG TGTIGAAVAE HLARTGESKH LLIVSRSGPA
1801 AHGAEELVSR IAEFGAEATF VAADVSEPDA VAALIEGIDP AHPLTGVVHA
1851 AGVLDNALIG SQTTESLTRV WAAKAAAAQQ LHEATRESRL GLFVMFSSFA
1901 STMGTPGQAN YSAANAYCDA LAALRRAEGL AGLSVAWGLW EATSGLTGTL
1951 SAADRARIDR YGIRPTSAAR GCALLAAARA HGRPDLLAMD LDARVPAASD
2001 APVPAVLRTL AAAGAPATAR PTAAAAADGA TDWSGRLAGL TEEARLELLT
2051 ELVCTHAAGV LGHADAGAVQ VDAPFKELGF DSLTAVELRN RIAAATGLKL
2101 PAALVFDYPQ ARVLAAHLAE RLVPEGAGAM GGVSGAEGVR DAYGAGGPGG
2151 DMTAQVLLEV ARVEHTLSAA VPHGLDRAAV AARLEALLAR CTATTAATGA
2201 AGAAVEGDGD SDGDGAVDQL ETATAEQVLD FIDNELGV*

MonAIII, polyketide synthase multi-enzyme MONS3, housing extension modules 3 and 4 Length: 4133 amino acids

1 MVSEEKLVDY LKRVSADLHA TRQRLREAEE RGQEPVAVVE AACRYPGGIR
51 TPEDLWDLVA AGGNALGAFP DNRGWDLRRL FHPDPDHPGT TYAREGGFLH
101 DADLFDPEFF GISPREAAVL DPQQRLLLEC AWEALERAGI DPRSLQGSRT
151 GVYAGAALPG FGTPHIDPAA EGHLVTGSAP SVLSGRLAYT FGLEGPAVTI
201 DTACSSSLVA VHLAAHALRQ RECDLALAGG VTVMTTPYVF TEFSRQRGLA
251 ADGRCKPFAA AADGTAFSEG AGLLVLERLS DARRAGHRVL AVIRGSAVNQ
301 DGASNGLTAP NGPAQQRVIR AALAGARLSP AEVDAVEAHG TGTRLGDPIE
351 ADALLATYGQ ERHGGRPLWL GSVKSNIGHT QGAAGAAGLI KMVQALRHET
401 LPATLYADEP TPHADWESGA VRLLSAPVAW PRGEHGEHTR RAGISSFGIS
451 GTNAHLILEE APAADAEGAG GDGDGDGGGV RPVVRVGATG PREEQGQGQG
501 QEQHQQQRQQ RQRSSMMPTP HLPWLLSARS PAALRAQADA LANHVAHADH
551 SIADIGGTLL RRTLFEHRAV VLGTDRDERA AALAALAAGR AHPALTRAAG
601 PARNGGTAFL FTGQGSQRPG MGRQLYDTFD VFAESLDETC ARLDPLLEQP
651 LKPVLFAPAD TAQAAVLHGT GMTQAALFAL EVALYRQVTS FGIAPSHLTG
701 HSVGEIAAAH VAGVFSLADA CTLVAARGRL MQALPAGGAM LAVQAAEDDV
751 LPLLAGQEER LSLAAVNGPT AVVVSGEAAA VGEVEKALRG RGLKTKRLNV
801 SHAFHSPLIE PMLDDFREVA RGLTFHAPTL PVVSNLTGRL ADAELMADAE
851 YWVRHVRRPV RFHDGLRALS EQGVVRYLEL GPDPVLATMV QDGLPAPAEG
901 EEPEPVVAAA LRSKHDEGRT LLGAVAALHT DGQPADLTAL FPADAGQVPL
951 PTYRFQRRRY WRVAPDAAAP ARAAGLQETG HPLLPAVIRQ ADGGILLAGR
1001 LSLRTHPWLA DHTIAGGVPL PATAFVELAL LAGRHAACDT IDDLTLETPL
1051 LLDDTGTGVG AAVGAGADAL VDAIEVQLAL GAPDGSGRRA LTVHSRPADD
1101 AADDGDAADA ADAAGRGGPG GSGDLGDPGD PGDLGDGGGS RGWRRHATGI

1151 LSAGPAAEPA APDAAPWPPA DATALDVDAL YARLDAQGYS YGPAFRAVHA

1201 AWRHGDDLYA DVRLADEQRA EADAFALHPA LLDAALHAVD ELYRGSEGRG

1251 QEQGQGGQEP EQGRGDADAP VRLPFSFSDI RHHATGATRL WVRLSPQGDD

1301 RLRLSLTDGE GGQVATVDAL QLRLIPADRW RAARPTTAAP LYHLDWHELP

1351 LPEPAETDPA AHSWAVLGAH DAGLAPAAHY PDLAALKAAV EAGEPVPDIV

1401 FAPFPAQGTE TDVPAQVRAH ARHALELLRD WLTTEAFAAA RLVVLTTGAV

1451 TARPEDGPAD LATAPVWGLV RAAQAEQPDH VVLVDIDKDI DKDTDEETDQ

1501 ATDAGTASRH ALPAALAAAA AQAETQLALR AGTVLVPRLA VVPPRTDTPA

1551 LHATAPESTT DTVDSTGIAG AAESGGTVLI TGGTGGLGQA VARHLAAAHG

1601 ARHLLLVSRR GDAAEGVAEL RADLADDGVD VRVAACDITD RDALAGLLAD

1651 IPAAHPLTAV VHTAGVIDDS LITAMTPERL DAVLAPKADA AWHLHELTRD

1701 KDLSAFVLFS SGASVLGNGG QANYAAANTF LNTLAEHRRA AGLAATSVAW

1751 GLWESASGGM AARLGDADRA RIHRTGVTGL TDEQALALFD AALTAEHPTV

1801 LATRFDRAVL RGQAAARTLQ PALRGLVRTP RPTASAGAIG STAATGSATD

1851 ENAPSSWAAR LARLSAADRD RALNELIREQ IATVLAHPSP DTIELGRAFQ

1901 ELGFDSLTAL ELRNRLSTAT GIRLPATLVF DHPSPTALVR HLHSHLPDEA

1951 QHTSPTAPGA SAEGTAATAT GIDDDPIAIV GMACRYPGGV TSPEQLWQLV

2001 ATGTDAIGPF PEDRGWDTAG LFDPDPDQVG HSYTREGGFL YDAARFDAGF

2051 FGISPREAAA TDPQQRLLLE TAWQAFEHAG IDPAALRGTP CGVITGIMYD

2101 DYGSRFLARK PDGFEGRIMT GSTPSVASGR VAYTFGLEGP AITVDTACSS

2151 SLVAMHLAAQ ALRQGECELA LAGGVTVMAT PNTFVEFSRQ RGLAPDGRCK

2201 PFAAAADGTG WGEGAGLVVL ERLSDARRKG HRVLALLRGS AVNQDGASNG

2251 MTAPNGPSQE RVIRTALAGA GRGPEDIDVV EAHGTGTTLG DPIEAQALLA

2301 TYGQGRPEDR PLWLGSVKSN IGHTQAAAGV AGVIKMVMAL RHEQLPTTLH

2351 ADEPTPHVQW DGGGVRLLTE PVPWSRGERT RRAGVSSFGI SGTNAHLILE
2401 EPPEEDLPEP VAAEPGGVVP WVVSGRTPDA LREQARRLGE FVVGAGDVSA
2451 AEVGWSLATT RSVFEHRAVV AGRDRDDLVA GMQALAAGET PTDVVSGAAA
2501 SSGAGPVLVF PGQGSQWVGM GAQLLDESPV FAARIAECEQ ALSAYVDWSL
2551 SDVLRGDGSE LSRVEVVQPV LWAVMVSLAA VWADYGVTPA AVVGHSQGEM
2601 AAACVAGALS LEDAARIVAV RSDALRQLQG HGDMASLGTG AEQAAELIGD
2651 RPGVVVAAVN GPSSTVISGP PEHVAAVVAE AEARGLRARV IDVGYASHGP
2701 QIDQLHDLLT EGLADIRPAN TDVAFYSTVT AERLTDTTAL DTDYWVTNLR
2751 QPVRFADTIE ALLADGYRLF IEASAHPVLG LGMEETIEQA DIPATVVPTL
2801 RRDHGDTTQL TRAAAHAFTA GADVDWRRWF PADPTPRTVD LPTYAFQHQH
2851 YWLEEPSGLT GDAADLGMVA AGHPLLGACV ELAESDSYLF TGRLSRRAPS
2901 WLAEHVVAGT VLVPGAALVE WVLRAGDEAG CPTIEELTLQ APLVLPESGG
2951 LQVQVVVGAT DEQSGRRDVH VYSRSEQDAS AVWVCHAVGV VSSEMPEAAA
3001 ELSGQWPPAG AEAVDVEDFY ARAAEAGYAY GPAFQGLRAL WRHGTELFAE
3051 VVLPEQAGGH DGFGIHPALL DAALHPLMLL DRPADGQMWL PFAWSGVSLN
3101 ADRATHVRVR LSPRGEAAER DLRVVIADAT GAPVLTVDAL TLRAADPGRL
3151 GAAARGGVDG LYTVDWTPLP LPQPLPLPRT DAGGSADWVI LSDNSSAALA
3201 DAVSSATAAG GGAPWALLAP VGGGSADDGL PVVRRTLSLV QEFLAAPELT
3251 ESRLVIVTRG AVATDADGDV AASAAAVWGL IRSAQSENPG RFVLLDVEEE
3301 HLHPDGGELP YAALRHAVEE LDEPQLALRS GKFLVPRMTP AAAPEELVPP
3351 VGTSGWRLGT SGTATLENLS VIDAPEAFAP LEPGQVRISV RAAGMNFRDV
3401 LIALGMYPDK GTFAGSEGAG HVTEVGPGVT HLSVGDRVMG LFEGAFAPLA
3451 VADARMVVPI PEGWSFQEAA AVPVVFLTAW YGLVDLGRLR AGESLLIHAG
3501 TGGVGMAATQ IARHLGAEVF ATASPAKHGV LDGMGIDAAH RASSRDLDFE

3551 ETLRAATGGR GMDVVLNSLA GEFTDASLRL LAEGGRMVDM GKTDKRDPDR
3601 VAAEHAGAWY RAFDLVPHAG PDRIGEMLAE LGELFASGAL APLPVQTWPL
3651 GRAREAFRFM SQAKHTGKLV LEIPPALDPD GTVLITGGTG VLAAAVAEHL
3701 VREWGVRHLL LAGRRGSEAP GSSELAEELT ELGAEVTFAA ADVSDPDAVA
3751 ELVGKTDPAH PLTGVIHAAG VLDDAVVTAQ TPESLARVWA AKATAAHLLH
3801 EATREARLGL FLVFSSAAAT LGSPGQANYA AANAYCDALV RQRRAEGLAG
3851 LSIGWGLWQT ASGMTGHLGE TDLARMKRTG FTPLTTEGGL ALLDAARAHG
3901 RPHVVAVDLD ARAVAAQPAP SRPALLRALA AGATPGARTA RRTAAAGSVA
3951 PAGGLADRLA GLPHPERRRL LLDLVRGNVA GVLGHSDHDA VRPDTSFKEL
4001 GFDSLTAVEL RNRLAAATGL KLPAALVFDY PESATLVDHL LERLSPDGAP
4051 PPVKDAADPV LNDLGRIESS LDALALDADA RSRVTRRLNT LLSKLNGAAT
4101 AGSPADVTDL DALDALDDVS DDEMFEFIDR EL*

MonAIV, polyketide synthase multi-enzyme MONS4, housing extension modules 5 and 6 Length: 4039 amino acids

1 MSSAEESSPD VSGTGVSGTG ESATGTSSTE AKLRQYLKRV TVDLGQARRR
51 LREVEERAQE PIAIVSMACR FPGDTRTPEA LWDLVAEGGD AIDDFPTNRG
101 WDLESLYHPD PDHPGTSYVR RGGFLYDAPA FDASFFGISP REALAMDPQQ
151 RVLMETAWQL LERAGIDPAS LKLSATGVYI GAGVLGFGGA QPDKTVEGHL
201 LTGSALSVLS GRISFTLGLE GPSVSVDTAC SSSLVSMHLA AQALRQGECD
251 LALAGGVTVM STPGAFTEFS RQGALSPDGR SKAFAASADG TGFSEGAGLL
301 LLERLSDARR NGHKVLAVIR GSAVNQDGAS NGLTAPNGPS QERVIRAALA
351 NAGLGAAEVD AVEAHGTGTK LGDPIEAGAL LATYGRDRDE DRPLWLGSVK
401 SNIGHPQGAA GVAGVIKMVM ALQRELLPAT LYVDEPTPHV DWSSGSVRLL
451 TEPVPWTRGE RPRRAGVSAF GMSGTNAHVI LEEAPPEEAA AAETPAEGTG
501 AVVPWVVSGR GEEALRAQAA QLAEHVRDDD QRPASPLEVG WSLATTRSVF

551 ENRAVVVGDD RDALLDGLRS LAAGEASPDV VSGAVGPTGP GPVMVFPGQG

601 GQWVGMGARL LDESPVFAAR IAECEQALSA YVDWSLTDVL RGDGSELARI

651 DVVQPVLWAV MVALAAVWAD QGIEPAAVVG HSQGEIAAAC VVGAISLDEA

701 ARIVAVRSVL LRQLSGRGGM ASLGMGQEQA ADLIDGHPGV VVAAVNGPSS

751 TVISGPPEGI AAVVADAQER GLRARAVASD VAGHGPQLDA ILDQLTEGLA

801 GIRPAATDVA FYSTVTAGHL TDTTELDTAY WVRNVRRTVR FADTIDALLA

851 DGYRLFIEVS PHPVLNLALE GLIERAAVPA TVVPTLRRDH GDTTQLARAA

901 AHAFAAGADV DWRRWFPADP APRTVDLPTY AFQRQDFWPA PAGGRSGDPA

951 GLGLAASGHP LLGASVGLAS GDVHLLSGRV SRQSAAWLDD HVVAGQALVP

1001 GAAQVEWVLR AGDDAGCSAL EELTLQTPLV LPDTGGLRIQ VVVEAADAHG

1051 RRDVRLFSRP DDDDAFASTH PWTCHATGVL APAPTDGTNG TRDAADTLDG

1101 AWPPADAEPV PADDLYAQAD RTGYGYGPAF RGVRALWRHG KDVLAEVTLP

1151 KEAGDPDGFG IHPALLDAVL QPAALLLPPT DAEQVWLPFA WNDVALHAVR

1201 ATTVRVRLTP LGERIDQGLR ITVADAVGAP VLTVRDLRSR PTDTGRLAAA

1251 ATRDRHGLFD LEWIAPENAA ENAAGPARDA SEGWVTLGED AASLADLLAS

1301 VEAGAPAPQL VAAPVEPDRT DDGLALATHV LDLVQTWLAS PLHDSRLVLV

1351 TRGAVTDADV DVAAAAVWGL VRSAQSEHPG RFTLIDLGPD DTLAAAMQAA

1401 HLEEPQLAVH GGEIRVPRLV RATTDPTAPN GTPEADRTAD PSEGLHRNGT

1451 VLITGGTGVL GRLVAEHLVT EWGVRHLLLA SRRGDQAPGS AELRARLSEL

1501 GASVEIAPAD VGDAEAVAAL IASVDPAHPL TGVIHAAGVL DDAVITAQTP

1551 ESLARVWATK ATAARHLHEA TRETPLDFFV VFSSAAASLG SPGQANYAAA

1601 NAYCDALVQH RRAQGLAGLS IAWGLWQATS GMTGQLSETD LARMKRTGFA

1651 ALTDEGGLAL LDAARAHDRA YVVAADLDPR AVTDGLSPLL RALTAPATRR

1701 RVASEGLADG ALATRLAGLD ADGRLRLLTD VVREYVAAVL GHGSAARVGV

1751 DIAFKDLGFD SLTAVELRNR LSAACDVRLP ATLIFDHPTP QALATHLVDR
1801 LAGSTSATTT VNATAPAAAH VAAGADVDAD TDDPVAIVAM TCRFPGGVAS
1851 PDDLWDLLDA RKDAMGAFPT DRGWDLERLF HPDPDHPGTS YTDQGGFLPD
1901 AGDFDAAFFG INPREALAMD PQQRLLLEAS WEVLERAGID PTTLKGTPTG
1951 TYVGLMYHDY AKSFPTADAQ LEGYSYLAST GSMVSGRVAY TLGLEGPAVT
2001 VDTACSSSLV SIHLATQALR HGECDLALAG GVTVMADPDM FAGFSRQRGL
2051 SPDGRCKAYA AAADGVGFSE GVGVLLLERL SDARRHGRRV LGVVRGSAVN
2101 QDGASNGLTA PNGPSQERVI RQALASGGLS SVDVDVVEGH GTGTTLGDPI
2151 EAQALLATYG QGRPEDRPLW LGSVKSNIGH TQAAAGVAGV IKMVMAMRHG
2201 VVPASLHVDV PSPHVEWDSG AVRLAVESVP WPQVEGRPRR AGVSSFGASG
2251 TNAHVIVESV PDGLEEDSVS VGGEALETET DGRLVPWVVS ARSPQALRDQ
2301 ALRLRDFASD ASFRAPLADV GWSLLKTRAL HEHRAVVVGA ERAELIAALE
2351 ALATGEPHAA LVGPACSQAR VGGDDVVWLF SGQGSQLVGM GAGLYERFPV
2401 FAAAFDEVCG LLEGPLGVEA GGLREVVFRG PRERLDHTVW AQAGLFALQV
2451 GLARLWESVG VRPDVVLGHS IGEIAAAHVA GVFDLADACR VVGARARLMG
2501 GLPEGGAMCA VQATPAELAA DVDGSAVSVA AVNTPDSTVI SGPSDEVDRI
2551 AGVWRERGRK TKALSVSHAF HSALMEPMLA EFTEAIRGVK FRQPSIPLMS
2601 NVSGERAGEE ITDPEYWARH VRNAVLFQPA IAQVADSAGV FVELGPAPVL
2651 TTAAQHTLDE SDSQESVLVA SLAGERPEES AFVEAMARLH TAGVAVDWSV
2701 LFAGDRVPGL VELPTYAFQR ERFWLSGRSG GGDAATLGLV AAGHPLLGAA
2751 VEFADRGGCL LTGRLSRSGV SWLADHVVAG AVLVPGAALV EWALRAGDEV
2801 GCVTVEELML QAPLVVPEAS GLRVQVVVEE AGEDGRRGVQ IYSRPDADAV
2851 GGDDSWICHA TGVLSPESAR LDTELGGVWP PAGAEPLDVD GFYAQAGEAG
2901 YGYGPAFRGL RAVWRHGQDL LAEVVLPEAA GAHDGYGIHP ALLDATLHPL

2951 LAARFMDGSE DDQLYVPFGW AGVSLRAVGA TTVRVRLRPV GESVDQGLSV
3001 TVTDATGGPV LSVDSLQTRP VKPSQLAAAQ QPDVRGLFTV EWTPLPQTDA
3051 DGEADWVVLS DGVGRLADVV SAAGGEAPWA VVAPVDASVG DGREGLDGRL
3101 VVERVLSLVQ EFLALPELAE SRLLVVTRGA VATGVDGDGD VDASAAAVWG
3151 LVRSAQSENP GRFILLDVDG DGDDQGPDLN GRHLPHATLR HAAEELDEPQ
3201 LALREGTLYV PRLTQARQSA ELVVPPGEPA WRLRMVHDGS LDALAAVACP
3251 EALEPLAPGQ VRIAVHAAGI NFRDVLVALG MVPAYGAMGG EGAGVVTEVG
3301 PEVTHVSVGD RVMGVFEGAF GPVVIAEARM VTPVPQGWDM REAAGIPAAF
3351 LTAWYGLVEL AGLKAGERVL VHAATGGVGM AAVQIARHVG AEVFATASPG
3401 KHAVLEEMGI DAAHRASSRD LAFEGTFREA TGGRGMDVVL NSLAGEFIDA
3451 SLRLLGDGGR FLEMGKTDVR AAEEVAAEHA DVSYTAYDLV GDAGPDRISN
3501 MLDKLVELFA SERLKPLPVR SWPLDKAQEA FRFMSQAKHT GKLVLEIPPA
3551 LDPEGTVLVT GGTGALGQVV AEHLVREWGV RHLLLASRRG PEAPGSDELA
3601 SKLTGLGAEV TIVAADVSDP ASVVELVGKT DPSHPLTGVV HAAGVLEDGV
3651 VTAQTPEGLA RVWAAKAAAA ANLHEATREM RLGLFVVFSS AAATLGSPGQ
3701 ANYAAANAYC DALMQHRRAV GQVGLSVGWG LWEAPDAKPG VAADAKASAA
3751 TVGKASALSD GTNGSAPQDT TGTAPQGMTG GLTDTDVARM ARIGVKGMSN
3801 AHGLALFDAA HRHGRPHLVG FNLDLRTLAT HPLHTRPALL RGLATPTAGG
3851 ASRPTATAGG QPADLAGRLA ALSPSDRHHT LVRLIREQAA TVLGHHPDSL
3901 TTGSTFKELG FDSLTAVELR NRLSAATGLR LPAGLVFDHP DADILAEHLG
3951 AQLAPDGDTP AGAEATDPVL RDLAKLENAL SSTLVEHLDA DAVTARLEAL
4001 LSNWKAASAA PGSGSTKEQL QVATTDQVLD FIDKELGV*

MonAV, polyketide synthase multi-enzyme MONS5, housing extension modules 7 and 8 Length: 4107 amino acids

1 MASEEELVDY LKRVAAELHD TRQRLREVED RRQEPVAVVG MACRFPGGIE
51 TPEGLWELVA AGDDAIEPFP TDRGWDLEGI YHPDPDHPGT CYVREGGFLA
101 APDRFDSDFF GFSPREALAS SPQLRLLLET SWEALERAGI NPASLKGSPT
151 GVYVGAATTG NQTQGDPGGK ATEGYAGTAP SVLSGRLSFT LGLEGPAVTV
201 ETACSSSLVA MHLAANALRQ GECDLALAGG VTVMSTPEVF TGFSRQRGLA
251 PDGRCKPFAA AADGTGWGEG AGLILLERLS DARRKGHKVL AVIRGSAINQ
301 DGASNGFTAP NGPSQRRVIR QALSSAHLST SEIDVVEAHG TGTRLGDPIE
351 AEALIATYGK EREDDRPLWL GSVKSNIGHT QAAAGVAGVI KMVMALQREL
401 LPATLNVDEP TPHVQWEGGG VRLLTEPVPW SRGERPRRAG ISSFGISGTN
451 AHVVLEEAPP EEDVPGPVAA EPEGVVPWVV SARTEEALSE QARRLGEFVA
501 DTDPSTADVG WSLTTSRAIL EHRAVVVGRD RDALTAGLAA LAAGEESADV
551 VAGVAGDVGP GPVLVFPGQG SQWVGMGAQL LDESPVFAAR IAECEQALSA
601 YVDWSLSAVL RGDGSELSRV EVVQPVLWAV MVSLAAVWAD YGVTPAAVIG
651 HSQGEMAAAC VAGALSLEDA ARVVAVRSDA LRQLMGQGDM ASLGASSEQA
701 AELIGDRPGV CIAAVNGPSS TVISGPPEHV AAVVADAEER GLRARVIDVG
751 YASHGPQIDQ LHDLLTDRLA DIRPATTDVA FYSTVTAERL TDTTALDTDY
801 WVTNLRQPVR FADTIDALLA DGYRLFIEAS AHPVLGLGME ETIEQADIPA
851 TVVPTLRRDH GDTTQLTRAA AHAFTAGATV DWRRWFPADP TPRTIDLPTY
901 AFQRRSYWLP VDGVGDVRSA GLRRVEHSLL PAALGLADGA LVLTGRLAAS
951 GGGGGWLADH AVAGTTLVPG AALVEWALRA ADEAGCPSLE ELTLQAPLVL
1001 PGSGGLQVQV VVGPADGQGG RREVRVFSRV DSDDEAAGQD EGWSCHATGV
1051 LSPEPGAVPD GLSGQWPPTG AEPLEISDLY EQAASAGYEY GPSFRGLRSV
1101 WRHGHNLLAE VELPEQAGAH DDFGIHPVLL DAALHPALLL DQNAPGEEQE
1151 PAQPALRLPF VWNGVSLWAT GAATVRVRLA PHGGGETDDS AGLRVTVADA

1201 TGAPVLSVDS LALRPADPEL LRTAGRAGSG TNGLFTVEWT ALPPADVADH

1251 AAGDGWAVLG QDVPDWAGAD MPRHPDMASL SAALDEGTQA PAAVFVETTA

1301 TSHATPNTAA DVTLDASGRA VAERTLHLLR DWLAEPRLAE TRLVLITHHA

1351 VTTPADDDVN AAPLDVPAAA LWGLIRSAQA EHPDRFVLLD TDAKANTDPG

1401 PDTSTDHSTA SGTYRTVIAR ALATGEPQLA VRAGELLAPR LARAATPTPE

1451 TPTPETQPDT GSGSEAGAGS GSGPGATLDP DGTVLIAGGT GMMGGLVAEH

1501 LVRAWSVRHL LLVSRQGPDA PDARDLADRL VGLGATVRIV AADLTDGRAT

1551 ADLVASVDPA HPLTGVIHAA GVLDDAVVTA QTSDQLARVW AAKASVAANL

1601 DAATSELPLG LFLMFSSAAG VLGNAGQAGY AAANAFVDAL VGRRRATGLP

1651 GLSIAWGLWA RGSAMTRHLD DADLARLRAG GVKPLLDEQG LALLDAARAT

1701 AAHTSLVVAA GIDVRGLNRD DVPAILRDLA GRTRRRAAAD STVDQAALER

1751 RLTGLDEAER RAVVTDVVRE CVAAVLGHRS AADVRTEANF KDLGFDSLTA

1801 VQLRNRLSAA SGLRLPATLA FDHPTPQALA AYLGTRLSGR TATPVAPVAP

1851 SAAATDEPVA IVAMACKYPG GATSPEGLWD LVAEGVDAVG AFPTGRGWDL

1901 ERLFHPDPDH PGTSYADEGA FLPDAGDFDA AFFGINPREA LAMDPQQRLL

1951 LEASWEVLER AGIDPTTLKG TPTGTYVGVM YHDYAAGLAQ DAQLEGYSML

2001 AGSGSVVSGR VAYTLGLEGP AVTVDTACSS SLVSIHLAAQ ALRQGECTLA

2051 LAGGVTVMAT PEVFTGFSRQ RGLAPDGRCK PFAAAADGTG WGEGVGVLLL

2101 ERLSDARRHG RRVLGVVRGS AVNQDGASNG LTAPNGPSQE RVIRQALASG

2151 GLSSVDVDVV EGHGTGTTLG DPIEAQALLA TYGQGRPVDR PLWLGSVKSN

2201 IGHTQAAAGV AGVIKMVMAM RHGVVPASLH VDVPSPHVEW DSGAVRLAVE

2251 SVPWPEVEGR PRRAGVSSFG ASGTNAHVIV ESVPDGLGED SVSVSGEAPE

2301 TETDGRLVPW VVSARSPQAL RDQALRLRDA VAADSTVSVQ DVGWSLLKTR

2351 ALFEQRAVVV GRERAELLSG LAVLAAGEEH PAVTRSREDG VAASGAVVWL

2401 FSGQGSQLVG MGAGLYERFP VFAAAFDEVC GLLEGPLGVE AGGLREVVFR
2451 GPRERLDHTM WAQAGLFALQ VGLARLWESV GVRPDVVLGH SIGEIAAAHV
2501 AGVFDLADAC RVVGARARLM GGLPEGGAMC AVQATPAELA ADVDDSGVSV
2551 AAVNTPDSTV ISGPSGEVDR IAGVWRERGR KTKALSVSHA FHSALMEPML
2601 AEFTEAIREV KFTRPKVSLI SNVSGLEAGE EIASPEYWAR HVRQTVLFQP
2651 GIAQVASTAG VFVELGPGPV LTTAAQHTLD DVTDRHGPEP VLVSSLAGER
2701 PEESAFVEAM ARLHTAGVAV DWSVLFAGDR VPGLVELPTY AFQRERFWLS
2751 GRSGGGDAAT LGLVAAGHPL LGAAVEFADR GGCLLTGRLS RSGVSWLADH
2801 VVAGAVLVPG AALVEWALRA GDEVGCVTVE ELMLQAPLVV PEASGLRVQV
2851 VVEEAGEDGR RGVQIYSRPD ADAVSGDDSW ICHATGTLTP QHTDAPNDGL
2901 AGAWPAAGAV PVDLAGFYER VADAGYAYGP GFQGLRAVWR HGQDLLAEVV
2951 LPEAAGAHDG YGIHPALLDA TLHPALLLDW PGEVQDDDGK VWLPFTWNQV
3001 SLRAAGAATV RVRLSPGEHD EAEREVQVLV ADATGTDVLS VGSVTLRPAD
3051 IRQLQAVPGH DDGLFSVDWT PLPLSRTDVS QTDADGDADW VVLSDGVGSL
3101 ADVVSAAGGE APWAVVAPVG ASAGGGLAGF DRREGLDGRL VVERVLSLVQ
3151 EFLAAPELAE SRLLVLTRGA VATGGDGDGD VDASAAAVWG LVRSAQSENP
3201 GRFILLDVDM DVDVDVDMDV DVDVDVDVDV DGDGNGSDLD PDLNGRRLPH
3251 ATLRHAAEEL DEPQLALRDG QLLVPRLVRA TGGGLVVAPT DRAWRLDKGS
3301 AETLESVAPV AYPGVMEPLG PGQVRLGIHA AGINFRDVLV SLGMVPGQVG
3351 LGGEGAGVVT ETGPDVTHLS VGDRVMGVLH GSFGPTAVAD TRMVAPVPQG
3401 WDMRQAAAMP VAYLTAWYGL VELAGLKAGE RVLIHAATGG VGMAAVQIAR
3451 HLGAEVFATA SAAKHVVLEE MGIDAAHRAS SRDLAFEDTF RQATDGRGMD
3501 VVLNSLTGEF IDASLRLLGD GGRFLEMGKT DVRTPEEVAA EYPGVTYTVY
3551 DLVTDAGPDR IAVMMSELGE RFASGALDPL PVRSWPLDKA REAFRFMSQA

3601 KHTGKLVLDV PAPLDPDGTV LITGGTGALG QVVAEHLVRE WGVRHLLLAS
3651 RRGLDAPGSG ELADRLSDLG AEVTVAAADV SDPASVVELV GKTDPSHPLT
3701 GVVHAAGVLE DGIVTAQTPE GLARVWAAKA AAAANLHEAT REMRLGLFVV
3751 FSSAAATLGS PGQANYAAAN AYCDALMQRR RAAGQVGLSV GWGLWEAPDA
3801 KPGVAADAKP DVAADAKTGV AADGTPQGMT GTLSGTDVAR MARIGVKAMT
3851 SAHGLALLDA AHRHGRPHLV AVDLDTRVLA HKPAPALPAL LRAFAGDQGG
3901 QGGGRGGGRG GGPARPAAAT TRQNVDWAAK LSVLTAEEQH RTLLDLVRTH
3951 AAAVLGHAGT DAVRADAAFQ DLGFDSLTAV ELRNRLSAST GLRLPATFIF
4001 RHPTPSAIAD ELRAQLAPAG ADPAAPLFGE LDKLETVITG HAHDESTRTR
4051 LAARLQNLLW RLDDTSARSD HAAGASDADG DAVENRDLES ASDDELFELI
4101 DRELPS*

MonAVI, polyketide synthase multi-enzyme MONS6, housing extension module 9 Length: 1701 amino acids

1 MPGTNDMPGT EDKLRHYLKR VTADLGQTRQ RLRDVEERQR EPIAIVAMAC
51 RYPGGVASPE QLWDLVASRG DAIEEFPADR GWDVAGLYHP DPDHPGTTYV
101 REAGFLRDAA RFDADFFGIN PREALAADPQ QRVLLEVSWE LFERAGIDPA
151 TLKDTLTGVY AGVSSQDHMS GSRVPPEVEG YATTGTLSSV ISGRIAYTFG
201 LEGPAVTLDT ACSASLVAIH LACQALRQGD CGLAVAGGVT VLSTPTAFVE
251 FSRQRGLAPD GRCKPFAEAA DGTGFSEGVG LILLERLSDA RRNGHQVLGV
301 VRGSAVNQDG ASNGLTAPND VAQERVIRQA LTNARVTPDA VDAVEAHGTG
351 TTLGDPIEGN ALLATYGKDR PADRPLWLGS VKSNIGHTQA AAGVAGVIKM
401 VMAMRHGELP ASLHIDRPTP HVDWEGGGVR LLTDPVPWPR ADRPRRAGVS
451 SFGISGTNAH LIVEQAPAPP DTADDAPEGA ATPGASDGLV VPWVVSARSP
501 QALRDQALRL RDFAGDASRA PLTDVGWSLL RSRALFEQRA VVAGRERAEL
551 LAGLAALAAG EEHPAVTRSR EEAAVAASGD VVWLFSGQGS QLVGMGAGLY

601 ERFPVFAAAF DEVCGLLEGE LGVGSGGLRE VVFWGPRERL DHTVWAQAGL
651 FALQVGLARL WESVGVRPDV VLGHSIGEIA AAHVAGVFDL ADACRVVGAR
701 ARLMGGLPEG GAMCAVQATP AELAADVDGS SVSVAAVNTP DSTVISGPSG
751 EVDRIAGVWR ERGRKTKALS VSHAFHSALM EPMLGEFTEA IRGVKFRQPS
801 IPLMSNVSGE RAGEEITSPE YWARHVRQTV LFQPGVAQVA AEARAFVELG
851 PGPVLTAAAQ HTLDHITEPE GPEPVVTASL HPDRPDDVAF AHAMADLHVA
901 GISVDWSAYF PDDPAPRTVD LPTYAFQGRR FWLADIAAPE AVSSTDGEEA
951 GFWAAVEGAD FQALCDTLHL KDDEHRAALE TVFPALSAWR RERRERSIVD
1001 AWRYRVDWRR VELPTPVPGA GTGPDADTGL GAWLIVAPTH GSGTWPQACA
1051 RALEEAGAPV RIVEAGPHAD RADMADLVQA WRASCADDTT QLGGVLSLLA
1101 LAEAPATSSD TTSHTSTSCG TGSLASHGLT GTLTLLHGLL DAGVEAPLWC
1151 ATRGAVSCGD ADPLVSPSQA PVWGLGRVAA LEHPELWGGL VDLPADPESL
1201 DASALYAVLR GDGGEDQVAL RRGAVLGRRL VPDATPDVAP GSSPDVSGGA
1251 AHADATSGEW QPHGAVLVTG GVGHLADQVV RWLAASGAEH VVLLDTGPAN
1301 SRGPGRNDDL AAEAAEHGTE LTVLRSLSEL TDVSVRPIRT VIHTSLPGEL
1351 APLAEVTPDA LGAAVSAAAR LSELPGIGSV ETVLFFSSVT ASLGSREHGA
1401 YAAANAYLDA LAQRAGADAA SPRTVSVGWG IWDLPDDGDV ARGAAGLSRR
1451 QGLPPLEPQL ALGALRAALD GGKGHTLVAD IEWERFAPLF TLARPTRLLD
1501 GIPAAQRVLD ASSESAEASE NASALRRELT ALPVRERTGA LLDLVRKQVA
1551 AVLRYEPGQD VAPEKAFKDL GFDSLVVVEL RNRLRAATGL RLPATLVYDY
1601 PTPRTLAAHL LDRVLPDGGA AELPVAAHLD DLEAALTDLP ADDPRRKGLV
1651 RRLQTLLWKQ PDAMGAAGPA DEEEQAAPED LSTASADDMF ALIDREWGTR
1701 *

MonH, probable regulatory protein Length: 981 amino acids

1 VSGVERGVGS AGPVEQGDGL AGLVERAEAL AALRGAFDGS PGTGGSLVVL
51 SGAVGTGKTA LLRAWADRIG ADADALVLTA TACRAERDLP LGVLEQLVRS
101 PGLPPASAER ALAWWDEEAS ATPGKTDANG TSANGTDANG TGAGQTGAGQ
151 AGVGQTGVGG EPVLAASALR GLCEVLRDLL AERPVVVAVD DAHHADAASL
201 QCLLSVVRRL RSARLHVLFT EYAHQKAQNA LLSSEFLHEP ALRRIRLEPL
251 SKAGVEALLA RHLDERTAQD LTPVVHGMSA GHPLLVRALA EDHRAAGGAG
301 EAYGRAVLSF LYRHETPVTQ VARAIAALGA HAGPGQVGRL LDVDAASVER
351 AVRQLTVAEV LHEGRLCHPA FAAAVLDGMP PEERRALHGR VADLLHEEGA
401 PATEVAAHLV AADRSDAPWA VPVFQEAAQL ALDEDQVETG VDYLRAAHQR
451 CRGAAQRAAV VGALADAEWR LDPAKVLRHL PDPAAMAPQT DPAALAPHTD
501 PAPTAAPTAA PTPTPIPTTP PLPTHLLWHG RVEEGLDAIG TLTGPGPNPA
551 GAPPMNPADL DTPWLWGAYL YPGHVKERLG SGALSPQRST PPAVTPELQG
601 AGTLMNDLLH GGERDATEAA ERALNRYRLG PRTIAVQTAA LAALTYRDRP
651 HRAAAWCDGL VAQADERNSP TWRALFTAWR ALLHLRQGDP AAAEQRAETA
701 LALLGSKGWG AAIGLPLAAA VQAKAALGDV DGAAALLERP VPQAVFQTRT
751 GLHYLAARGR YHLATGCHYA ALCDFYACGT RMSSWGVDLP ALEPWRLGAA
801 EAYLALGEGL LARQLVDGQL PLPTPDDGRT WGMTLRLRAA TSPAPARAEL
851 LDEAVAVLRE SGDTFELARA VADQAVAVRE GGEAERARLL ARKAELLARR
901 WGSAPAPATV PEPPERPGPA TPDAELTSAE RRVAELAAEG FTNREISRKL
951 CVTVSTVEQH LTRIYRKLDV RRLDLQAALG *

MonCI, flavin-dependent epoxidase Length: 496 amino acids

1 VTTTRPAHAV VLGASMAGTL AAHVLARHVD AVTVVERDAL PEEPQHRKGV
51 PQARHAHLLW SNGARLIEEM LPGTTDRLLA AGARRLGFPE DLVTLTGQGW
101 QHRFPATQFA LVASRPLLDL TVRQQALGAD NITVRQRTEA VELTGSGGGS

151 GGRVTGVVVR DLDSGRQEQL EADLVIDATG RGSRLKQWLA ALGVPALEED
201 VVDAGVAYAT RLFKAPPGAT THFPAVNIAA DDRVREPGRF GVVYPIEGGR
251 WLATLSCTRG AQLPTHEDEF IPFAENLNHP ILADLLRDAE PLTPVFGSRS
301 GANRRLYPER LEQWPDGLLV IGDSLTAFNP IYGHGMSSAA RCATTIDREF
351 ERSVQEGTGS ARAGTRALQK AIGAAVDDPW ILAATKDIDY VNCRVSATDP
401 RLIGVDTEQR LRFAEAITAA SIRSPKASEI VTDVMSLNAP QAELGSNRFL
451 MAMRADERLP ELTAPPFLPE ELAVVGLDAA TISPTPTPTP TAAVRS

MonBII, carbon-carbon double bond isomerase Length: 141 amino acids

1 MPDEAARKQM AVDYAERINA GDIEGVLDLF TDDIVFEDPV GRPPMVGKDD
51 LRRHLELAVS CGTHEVPDPP MTSMDDRFVV TPTTVTVQRP RPMTFRIVGI
101 VELDEHGLGR RVQAFWGVTD VTMDDPAGPA DTTHPEGIRA *

MonBI, carbon-carbon double bond isomerase Length: 144 amino acids

1 MNEFARKKRA LEHSRRINAG DLDAIIDLYA PDAVLEDPVG LPPVTGHDAL
51 RAHYEPLLAA HLREEAAEPV AGQDATHALI QISSVMDYLP VGPLYAERGW
101 LKAPDAPGTA RIHRTAMLVI RMDASGLIRH LKSYWGTSDL TVLG

MonAVIII, polyketide synthase multi-enzyme MONS8, housing extension modules 11 and 12 Length: 3754 amino acids

1 MSNEEKLLDH LKWVTAELRQ ARQRLHDKES TEPVAIVGMA CRYPGGARSA
51 EDLWELVRDG GDAVAGFPDD RGWDLESLYH PDPEHPATSY VRDGAFLYDA
101 GHFDAEFFGI SPREATAMDP QQRLLLETAW EAIEHAGMNP HALKGSDTGV
151 FTGVSAHDYL TLISQTASDV EGYIGTGNLG SVVSGRISYT VGLEGPAVTV
201 DTACSSSLVA IHLASQALRQ GECSLALAGG STVMATPGSF TEFSRQRGLA
251 PDGRCKPFAA AADGTGWGEG AGVVALELLS EARRRGHKVL AVIRGSATNQ
301 DGTSNGLAAP NGPSQERVIR AALANARLSA EDIDAVEAHG TGTTLGDPIE

351 AQALIATYGQ GRPEDRPLWL GSVKSNIGHT QAAAGVAGVI KMVMAMRNGL
401 LPTSLHIDAP SPHVQWEQGS VRLLSEPVDW PAERTRRAGI SAFGISGTNA
451 HLILEEAPPE EDAPGPVAAE PGGVVPWVVS GRTPDALREQ ARRLGEFAAG
501 LADASVSEVG WSLATTRALF DQRAVVVGRD LAQAGASLEA LAAGEASADV
551 VAGVAGDVGP GPVLVFPGQG SQWVGMGAQL LDESPVFAAR IAECEQALSA
601 HVDWSLSDVL RGDGSELSRV EVVQPVLWAV MVSLAAVWAD YGITPAAVIG
651 HSQGEMAAAC VAGALSLEDA ARIVAVRSDA LRQLQGHGDM ASLSTGAEQA
701 AELIGDRPGV VVAAVNGPSS TVISGPPEHV AAVVADAEAQ GLRARVIDVR
751 YASHGPQIDQ LHDLLTDRLA DIQPTTTDVA FYSTVTAERL DDTTALDTAY
801 WVTNLRQPVR FADTIEALLA DGYRLFIEAS PHPVLNLGIQ ETIEQQAGAA
851 GTAVTIPTLR RDHGDTTQLT RAAAHAFTAG APVDWRRWFP ADPTPRTVDL
901 PTYAFQHKHY WVEPPAAVAA VGGGHDPVEA RVWQAIEDLD IDALAGSLEI
951 EGQAESVGAL ESALPVLSAW RRRHREQSTV DSWRYQVTWK HLPDVPAPEL
1001 SGAWLLLVPA AHADHPAVLA TAQTLTAHGG EVRRHVVDAR AMERTELAQE
1051 LRVLMDGAAF AGVVNLLALD EEPHPEHSAV PAGLAATTAL VQALADNGAD
1101 IAVRTLTQGA VSTSAGDALT HPVQAQVWGL GRVAALEYPR LWGGLVDLPA
1151 RIDHQTLARL AAALVPQDED QISIRPSGVH ARRLAHAPAN TVGSGLGWRP
1201 DGTTLITGGT GGIGAVLARW LARAGAPHLL LTSRRGPDAP GAQELAAELT
1251 ELGAAVTVTA CDVGDREQVR RLIDDVPAEH PLTAVIHAAG VPNYIGLGDV
1301 SGAELDEVLR PKALAAHHLH ELTRELPLSA FVMFSSGAGV WGSGQQGAYG
1351 AANHFLDALA EHRRAEGLPA TSIAWGPWAE AGMAADQAAL TFFSRFGLHP
1401 LSPELCVKAL QQALDAGETT LTVANFDWAQ FTSTFTAQRP SPLLADLPEN
1451 RRASAPAAQQ EDATEASSLQ QELTEAKPAQ QRQLLLQHVR SQAAATLGHS
1501 DVDAVPATKP FQELGFDSLT AVELRNRLNK STGLTLPTTV VFDHPTPDAL

1551 TDVLRAELSG DAAASADPVR AAGASRGAAD DEPIAIVGMA CRYPGDVRSA
1601 EELWDLVAAG KDAMGAFPDD RGWDLETLYD PDPESRGTSY VREGGFLYDA
1651 GDFDAGFFGI SPREAVAMDP QQRLLLETAW EAIERAGLDR ETLKGSDAGV
1701 FTGLTIFDYL ALVGEQPTEV EGYIGTGNLG CVASGRVSYV LGLEGPAMTI
1751 DTGCSSSLVA IHQAAHALRQ GECSLALAGG ATVMATPGSF VEFSLQRGLA
1801 KDGRCKPFAA AADGTGWAEG VGLVVLERLS EARRNGHNVL AVIRGSAINQ
1851 DGTSNGLTAP NGQAQQRVIR QALANARLSA EDVDAVEAHG TGTMLGDPIE
1901 ASALVATYGK ERPADRPLWL GSIKSNIGHA QASAGVAGVI KMVMALRNEQ
1951 LPASLHIDAP TPHVDWDGSG VRLLSEPVSW PRGERPRRAG VSAFGISGTN
2001 AHLILEQAPD APEPVTAPAE DAAAPAGVVP WVVSARGEEA LRAQARLLAD
2051 RATADPRLAS PLDVGWSLVK TRSVFENRAV VVGKDRQTLL AGLRSLAAGE
2101 PSPDVVEGAV QGASGAGPVL VFPGQGSQWV GMGAQLLDES PVFAARIAEC
2151 ERALSAHVDW SLSAVLRGDG SELSRVEVVQ PVLWAVMVSL ASVWADYGIT
2201 PAAVIGHSQG EMAAACVAGA LSLEDAARIV AVRSDALRQL MGQGDMASLG
2251 AGSEQVAELI GDRPGVCVAA VNGPSSTVIS GPPEHVAAVV ADAEARGLRA
2301 RVIDVGYASH GPQIDQLHDL LTERLADIRP TTTDVAFYST VTAERLDDTT
2351 TLDTDYWVTN LRQPVRFADT IEALLADGYR LFIEASPHPV LNLGMEETIE
2401 RADMPATVVP TLRRDHGDAA QLTRAAAQAF GAGAEVDWTG WFPAVPLPRV
2451 VDLPTYAFQR ERFWLEGRRG LAGDPAGLGL ASAGHPLLGA AVELADGGSH
2501 LLTGRISPRD QAWLAEHRVM DTVLLPGSAF VELALQAAVR AGCAELAELT
2551 LHTPLAFGDE GAGAVDVQVV VGSVAEDGRR PVTVHSRPTG EGEEAVWTRH
2601 AAGVVAPPGP DAGDASFGGT WPPPGATPVG EQDPYGELAS YGYDFGPGSQ
2651 GLVSAWRLGD DLFAEVALPE AESGRADRYQ VHPVLLDATL HALILDAVTS
2701 SADTDQVLLP FSWSGLRVHA PGAEKLRVRI ARTAPDQLAL TAVDGGGGGE

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2751 PVLTLESLTV RPVAAHQIAG ARAADRDALF RLVWMEVAAR AEETGGGAPR
2801 AAVLAPVESG PMGGTSAGAL ADALSDALAA GPVWDTFGAL RDGVAAGGEA
2851 PDVVLAVCAA PGAGAGAVAD ADGRGGDPAG YARLATVSLL SLLKEWVDDP
2901 AFAATRLVVV TRGAVAARPG ETAGDLAGAS LWGLVRSAQA ENPGRLTLLD
2951 VDGLESSPAT LTGVLASGEP ELALRDGRAY VPRLVRDDAS VRLVPPVGSL
3001 TWRLARCQEA GGGQQLSLVD APEAGRALEP HEVRVAVRAA APGPLTAGQV
3051 EGAGVVTEVG GEVGSVAVGD RVMGLFDAVG PVAVTDAALL MPVPAGWSWA
3101 QAAGSLGAYV SAYHVLADVV APRGGETLLV GEETGSVGRA VLRLALAGRW
3151 RVEAVDGAST ADDSGAERAA DVTLRHEGAL VVHRAGGRPD EGQAVVPPEP
3201 GRVREILAEL TELTELAEIT ESAEPGLPAE RGDSRALTPL DITVWDIRQA
3251 PAAMAAPPSA GTTVFSLPPA FDPEGTVLVT GGTGALGSLT ARHLVERYGA
3301 RHLLLSSRRG ADAPGALELA ADLSALGARV TFAACDPGDR DEAAALLAAV
3351 PSDHPLTAVF HCAGTVNDAV VQNLTAEQVE EVMRVKADAA WHLHELTRDA
3401 DLSAFVLYSS VAGLLGGPGQ GSYTAANAFL DALARHRHDG GAAATSLAWG
3451 YWELASGMSG RLTDADRARH ARAGVVGLGA DEGLALLDAA WAGGLPLYAP
3501 VRLDLARMRR QAQSHPAPAL LRDLVRGGSK SGGGAVSAGA AALLKSLGAM
3551 SDPEREEALL DLVCTHIAAV LGYDAATPVN ATQGLRELGF DSLTAVELRN
3601 RLSAATGLKL PATFVFDHPN PAELAAQLRQ ELAPRAADPL ADVLAEFERI
3651 EDSLLSVSSK DGSARAELAG RLRATLARLD APQDTAGEVA VATRTRIQDA
3701 SADEIFAFID RDLGRDGASG QGNGQPTGQG NGHGNGNGNG NGNGHGQAVE
3751 GQR*

MonAVII, polyketide synthase multi-enzyme MONS7, housing extension module 10 Length: 1642 amino acids

1 MAHTEEKLLE YLKRVTADLR QTERRLQDVE SAGHEPVAVI GMACRLPGGV
51 RSPEEFWELV STGGDAVAPL PGNRNWDLDS LYDPDPESTG TSYVREGGFV

101 YDAGDFDPTF FGIGPTEAAA MAPQQRLALE TAWEAIERAG IDPLSLRSSD
151 TSTFIGCDGL DYALGASEVP EGTAGYFTIG NSGSVTSGRV AYTLGLEGPA
201 VTVDTACSSS LVSLHLATQA LRTQECSLAL AGGTYVMSSP APLIGFSELR
251 GLAPDGRCKP FSASSDGMGM AEGTGVVLLE RLSDARRKGH KVLAVIRGSA
301 INQDGASNGL TAPNGPAQER VIRAALANAR LAPEDIDAVE AHGTGTTLGD
351 PIEAGALISA YGRERPEDRP LWVGAVKSNI GHTQIAAGVA GVIKMVLALR
401 HDLLPAILHV DAPSPHVEWD GSGLRLLTDP VKWPRGERPR RAGVSSFGFS
451 GTNAHLILEE APPEEEDVPG SVAEEPGGVV PWVVSGRTPD ALRAQARRLG
501 EFAAGPADAS AADVGWSLTT TRSVFEHRAV VVGRDRDALT AGLGALAAGE
551 ASAGVVAGVA GDVGPGPVLV FPGQGSQWVG MGAQLLDESP VFAARIAECE
601 RALSAYVDWS LSAVLRGDGS ELSRVEVVQP VLWAVMVSLA AVWADYGVTP
651 AAVIGHSQGE MAAACVAGAL SLEDAARIVA VRSDALRRLQ GHGDMASLST
701 GAEQAAELIG DRPGVVVAAV NGPSSTVISG PPEHVAAVVA DAEARGLRAR
751 VIDVGYASHG PQIDQLHDLL TERLADIRPA NTDVAFYSTV TAERLTDTTA
801 LDTDYWVTNL RQPVRFADTI EALLADGYRL FIEASAHPVL GLGMEETIEQ
851 ADIPATVVPT LRRDHGDTTQ LTRAAAHAFT AGAPVDWRRW FPADPTPRTV
901 DLPTYAFQHQ HYWLERSASA SGAVSGEQSA AEAQLWHAVE ELDLGLLAET
951 LGSEEGSEEA VRALEPALPV LKGWRRRHQD QATIDSWRYR VTWKQRSDGP
1001 APELGGDWLL FVPADKAEHP AVRATAEALS EHGAAAVRLH PVETGRAGRQ
1051 ELAAVDTAGL AGIVNLLALD EEPHPEHPAV PAGLAATTAL LQALGDNGTT
1101 APLHTVTQGA VSTGATDPLT HPLQAHVWGL GRVAALEHPR LWAGLVDLPA
1151 RIDRHTLPRL AAALLPQDDE DQTAVRPTGI HHRRLTHAVG SIQNPVHSEA
1201 TWRPRGTTLI TGGTGGIGAV LARWLARQGA PRLHLTSRRG PDAPGARELA
1251 AELDGLGTAV TITACDVSDP RQLSGLIDDM PAEHPLTAVI HAAGMTDLTA

1301 IGDLTTARLG EVLGSKSDAA WNLHELTRDL DLSAFVMFSS GAGVWGSGQQ

1351 GAYGAANHFL DALAEHRRAQ GLPATSIAWG PWAEAGMSAD PESLTYFKRF

1401 GLLPIAPDLC VKALHQAVDA GDATLTVANF DWAKFTPTFT AQRPSPFLDD

1451 LPENQREAEQ TGTAAETSAF REELAKTPAS QRLGFLVQQV RTYAAATLGR

1501 TVEDIPAAKP FQELGFDSLT AVQLRNQLNT TTGLSLPATV IFDHPTPEAL

1551 ATHLRGQLGD GAEVAGEGDV LAALDKWDTA FGAAEVDEAA RRRIVGRLQV

1601 LVSKWSPAQD GPEGTDSAHA DLEAASADDI FDLISSEFGK S*

MonD, cytochrome P450 hydroxylase Length: 431 amino acids

1 VGLTVGPDNA KRGIVPITDS KPAATFPDLV DPSFWARPHA ERVALFEEMR

51 GLPRPAFIRQ NMPGVPWTFG YHALVKYADI VEVSRRPQDF SSNGATTIIG

101 LPPELDEYYG SMINMDNPEH SRLRRIVSRS FGRNMIPEFE AVATRTARRI

151 IDELIARGPG DFIRPVAAEM PIAVLSDMMG IPAEDHDFLF DRSNTIVGPL

201 DPDYVPDRAD SERAVIEASR ELGDYIAGLR AERLAAPGND LITKLVQVQA

251 DGEQLTRQEL VSFFILLVIA GMETTRNAIS HALVLLTEHP EQKQLLLSDF

301 DTHAPNAVEE ILRVSTPINW MRRVATRDCD MNGHRFRRGD RIFLFYWSGN

351 RDESVFPDPY RFDITRGTNA HVTFGAVGPH VCLGAHLARM EITVLYRELL

401 AALPQIHAVG QPRRLDSSFI EGIKHLHCAF *

MonRI, probable activator protein Length: 268 amino acids

1 VRYEMLGPLR IKDGNDYATI NAQKVEIVLT VLLIRADRVV SLEQLMREIW

51 GEDLPRRATA GLHVYISQLR KFLKVPGSAG NPVETRAPGY VLHKRDDDQI

101 DAQIFPELVD VGRSLLREKR FDEAASCFGQ ALALWRGPIL GQGGNGPGTN

151 GPIIDGFSTW LTEIRLECQE MLVECQLQLG RHREAVGMLY ALTAENPMCE

201 AFYRQLMLAL YRSERQADAL KVYQSVRKTL NDELGLEPGR PLQELQRAIL

251 AGDMHLMSPP PLALSGR*

MonAX, thioesterase Length: 278 amino acids

1 LSAFLAKGKI LSAFPPPDMS DPWIRRFRPR PEAVVRLVCF PHAGGSASYY
51 HPLAQSPTLP TDSEVLAVQY PGRQDRRRER LLDDIGELAD LITDALGPFD
101 DRPLAFFGHS MGAVLAYEVA QRLRERTGKQ PCRLFVSGRR APSRFRRGTV
151 HLLDDTELAA ELRRAGGTDP RFLDDEELLA EIIPVVRNDY RAVELYRWNP
201 SPPLSCPITA LVGDRDPQAP LDEVEAWQQH TEGPFDLKVF AGGHFYLNTH
251 QQGVTEVISK ALADSAQQRA TARGNAR*

ORF29, a homologue of CapK involved in cell wall biosynthesis Length: 428 amino acids

1 LADLVAHARS ASPYYRELYH GLPERIEDPT LLPVTDKKQL MDHFDDWPTD
51 RDITFEKVRA FTDDPELIGR RFLGRYLVAT TSGTSGRRGL FVLDDRYMNV
101 SSAVSSRVLA SWLGPLGIAR AVVHGGRFAQ LVATEGHYVG FAGYSRLRQD
151 GEARSKLVRA FSVHEPMSRL VAELNEYRPA FVIGYASTIM LFTAEQEAGR
201 LHIDPVLVEP AGETMTESDT DRIAAAFGAK VRTMYSATEC TYLSHGCAEG
251 WYHVNDDWAV LEPVDADHRP TPPGEFSHTT LISNLANRVQ PFLRYDLGDS
301 VMLRPDPCPC GTPSPAIRVQ GRSGDILTFP SGRGDDVSLA PLAFSSLFDR
351 MPGVELFQIE QTAPSTLRVR VVQAPGADAD HVWQRAHDGL THLLADNKLD
401 NVTVERGEEP PRQASGGKYR TIIPLAA*

LipB, lipase B Length: 338 amino acids

1 VKVPVEVTVR LSSWLGGLVA AVLAATVLPA SAASAADVSS PPLEIPAAEL
51 AKALHCGTEL GDLRDAGDKP TVLFVPGTGL KGEENYAWNY MAELKKKGYQ
101 SCWVDSPGRG LRDMQESVEY VVYATRAIQE ATGRKVDLVG HSQGGLLTAW
151 ALRFWPDLPG KVDDMVTLGS PFQGTRLASP CRPIAEVAGC PASVLQFARD
201 SNWSKALGAD GTPMPAGPSY TTIYSYADES VVADGEAPSL PGAHRIGVQD

251 ICPGRPWPTH IAMVVDQVSY DLVADAIEHP GPADTSRIDR AHCAKPVMPL

301 NSQEAVDALP GLLNFPIELL IHSQPWVDEE PPLRPYAR

ORF31, putative ion pump Length: 309 amino acids

1 MGHDHGPSAG AAGGTLSGTY RKRLLWTIGI SGSITVIQVV GALLSGSLAL

51 LADAAHSLTD AVGVSLALGA ITLAQRAPTP RRTFGFCRVE IFSAVLNALL

101 LVVIFAWVLW SAIGRFSEPV EVKGGLMFVV ALGGLAANLV GLWLLRDAKE

151 KSLNLRGAYL EVLGDALGSV AVIVGGLVIL LTGWQAADPI ASIVIGLLIV

201 PRAYGLLRDS LHVLLEATPQ DVDLGEVRRH LLEERGVVAV HDLHGWTVTS

251 GMPVLTAHVV VTEEALASGY GELLGRLQRC VGGHFDVAHS TIQLEPEGHV

301 EEDGALHT*

ORF32, hypothetical membrane protein Length: 364 amino acids

1 MTRALTLHDW IVAGIAVVAG VVAGLLLRAL LRWLGERASK TRWSGDDVIV

51 DALRTLVPCA AITAGLAAAA GALPLTPRTG RNVTMTLTAL LILAATLTAA

101 RIVTGLVKAV AQSRSGVAGS ATIFVNITRV VVLAMGFLIV LQTLGISIAP

151 LLTALGVGGL AVALALQDTL ANLFAGVHIL AAKTVQPGDY IQLSSGEEGY

201 VVDINWRNTT VRQLSNNLVI IPNAKLAGTN MTNYSRPEQE LSIMVQVGVS

251 YDSDLEQVEK VTTEVVDEVM AEITGAVPDH EAAIRFHTFG DSRISFTVIL

301 GVGEFSDQYR IKHEFIKRLH QRYRAEGIRV PAPVRTVRVQ QGELPPPLGI

351 PHQRDTSTQA RLH*

AmtA, glycine amidinotransferase (partial coding sequence) Length: 131 amino acids

1 MSPVNSHNEW DPLEEIIVGR LEGATIPSSH PVVACNIPTW AARLQGLAAG

51 FEYPQRLIEP AQQELDQFIA LLQSLDVTVR RPAAVDHKHR FGTPDWQSRG

101 FCNSCPRDSM LVVGDEIIET PMAWPCRCFE T

CLAIMS:

1. A DNA sequence which is (a) at least part of the sequence set out in the appended sequence listing; or (b) a variant of a sequence (a) which encodes a polypeptide which is at least 80%, preferably at least 90%, identical with the corresponding peptide as set out in table II; provided that it is not a sequence encoding all or part of the polypeptide consisting of amino acids 1-920 encoded by *mon AI* as set out in table II.

2. A DNA sequence according to claim 1 comprising the complete monensin gene cluster or a variant thereof.

3. A DNA sequence encoding at least part of at least one polypeptide which is necessary for the biosynthesis of monensin, and which is encoded by DNA included in the appended sequence listing or an allele, mutation or other variant thereof; provided that said polypeptide is not all or part of amino acids 1-920 encoded by *mon AI* as set out in table II.

4. A DNA sequence according to claim 3 which comprises at least part of one or more of the following genes: *mon BI, mon BII, mon CI, mon CII, mon H, mon RI, mon RII, mon T, mon AIX* and *mon AX*.

5. A DNA sequence according to claim 4 comprising all of the genes listed therein or an allele, mutation or other variant thereof.

6. A DNA sequence according to claim 3 encoding at least part of one or more of the polypeptides set out below, said polypeptide having the amino acid sequence as set out in the appended sequence data or being a variant thereof having the specified activity:

<u>peptide</u>	<u>activity</u>
mon CII	epoxyhydrolase/cyclase
mon E	S-adenosylmethionine-dependent methyltransferase
mon T	monensin resistance gene
mon RII	repressor protein
mon AIX	thioesterase
mon AI	polyketide synthase multienzyme
mon AII	polyketide synthase multienzyme
mon AIII	polyketide synthase multienzyme
mon AIV	polyketide synthase multienzyme
mon AV	polyketide synthase multienzyme
mon AVI	polyketide synthase multienzyme
mon AVII	polyketide synthase multienzyme
mon AVIII	polyketide synthase multienzyme
mon H	regulatory protein
mon CI	flavin-dependent epoxidase
mon BII	carbon-carbon double bond isomerase

mon BI	carbon-carbon double bond isomerase
mon D	cytochrome P450 hydroxylase
mon RI	activator protein
mon AX	thioesterase

7. A DNA sequence according to claim 6 encoding a single enzyme activity of a multienzyme encoded by any of *mon AI-mon AVIII* or a variant or part thereof.

8. A DNA sequence according to any preceding claim encoding any one or more of the domains as set out in Table I or a variant or part thereof.

9. A DNA sequence according to any preceding claim which has a length of at least 30, preferably at least 60, bases.

10. A recombinant cloning or expression vector comprising a DNA sequence according to any preceding claim.

11. A transformant host cell which has been transformed to contain a DNA sequence according to any of claims 1-9 and which is capable of expressing a corresponding polypeptide.

12. A hybridisation probe which is a DNA sequence according to any of claims 1-9.

13. Use of a probe according to claim 12 to detect a PKS cluster, optionally followed by isolation of the detected cluster.

14. Use of a probe according to claim 12 which encodes at least part of a polypeptide having a known function to detect genes encoding polypeptides having analogous function.

15. Use according to claim 14 wherein the polypeptide of known function is AT of module 5 or the regulatory protein encoded by *mon RI*.

16. A hybridization probe comprising a polynucleotide which binds specifically to a region of the monensin gene cluster selected from *mon BI, mon BII, mon CI, mon CII, mon H, mon RI, mon RII, mon T, mon AIX* and *mon AX*.

17. Use of a probe according to claim 16 in a method of detecting the presence of a gene cluster which governs the synthesis of a polyether, and optionally isolating a gene cluster detected thereby.

18. Use of a probe according to claim 12 which comprise a polynucleotide which binds specifically to a gene responsible for levels of activity of the monensin gene cluster, in a method of detecting an analogous gene in a gene cluster for biosynthesis of another polyketide, optionally followed by a step of manipulating the gene detected thereby to alter the level of expression of said other polyketide.

19. Use according to claim 18 wherein the gene is a regulatory gene, resistance gene or thioesterase gene.

20. Use of the *mon RI* gene or variant and a monensin promoter to control expression of a heterologous gene in *S. cinnamonensis*.

21. Use of a portion of the monensin gene cluster encoding a polypeptide having chain terminating activity, preferably comprising at least one of *mon AIX* and *mon AX* or a mutant, allele or other variant thereof encoding a polypeptide having chain terminating activity, to effect chain release of a peptide other than monensin.

22. Use of a portion of the monensin gene cluster encoding a polypeptide having carbon-carbon double bond isomerase activity, preferably comprising at least one of

mon BI and *mon BII* or a mutant, allele or other variant thereof having isomerase activity to provide a desired stereochemical outcome in the synthesis of a polyketide other than monensin.

23. A polypeptide encoded by a portion of the monensin gene cluster, preferably comprising at least one of *mon BI* and *mon BII* or a mutant, allele or other variant thereof, having carbon-carbon double bond isomerase activity, or at least one of *mon AIX* and *mon AX* or a mutant, allele or other variant thereof having chain terminating activity.

24. An epoxidase enzyme encoded by *mon CI* or a derivative or variant thereof having epoxidase activity.

25. A cyclase enzyme encoded by *mon CII* or a derivative or variant thereof having cyclase activity.

26. Use of a portion of the monensin gene cluster encoding a peptide having epoxidase or cyclase activity, preferably comprising *mon CI* or *mon CII* or a mutant, allele or other variant thereof encoding a polypeptide having epoxidase or cyclase activity to provide a said activity in the biosynthesis of a polypeptide other than monensin.

27. A process for producing a polyketide containing a desired starter unit comprising providing a PKS gene having a loading module and a plurality of extension modules, wherein the loading module includes a KS_q domain derived from a KS domain of a monensin extension module.

28. A process according to claim 27 wherein the KS_q domain is derived from KS of module 5 of monensin.

29. A process according to claim 27 or claim 28 wherein the starter unit also includes an AT_q domain derived from an AT domain which is naturally associated with the KS domain.

30. A DNA sequence comprising DNA encoding at least one PKS loading module and a plurality of PKS extension modules, and which can be expressed to produce a polyketide; wherein at least one of said modules or at least one domain thereof is a monensin module or domain or a variant thereof and is contiguous to a further one of said modules or a domain to which it is not naturally contiguous; provided that the sequence is not an ery loading module, the first and second extension modules of the ery PKS and the ery chain-terminating thioesterase in which the DNA encoding AT of the first extension module has been substituted by DNA encoding an ethyl malonyl-CoA

AT from the monensin gene cluster.

31. A DNA sequence according to claim 30 wherein said further module or domain is also a monensin module or domain or variant thereof.

32. A DNA sequence according to claim 30 wherein said further module or domain is a module or domain of a PKS of a polyketide other than monensin or a variant thereof.

33. A DNA sequence according to claim 30, 31 or 32 wherein said loading module is adapted to load a starter unit other than a starter unit normally received by the adjacent extension module.

34. A DNA sequence according to claim 33 wherein said loading module is derived from a monensin extension module or variant thereof.

35. A polyketide synthase encoded by the DNA sequence of any of claims 30-34.

36. A polyketide compound as produced by a synthase according to claim 35.

37. A vector containing a DNA sequence of any of claims 30-34.

38. A transformant cell transformed to contain a DNA sequence of any of claims 30-34.

39. A method of producing *S. cinnamonensis* capable of enhanced levels of production of monensin comprising engineering it to overexpress the *mon RI* gene.

40. A method according to claim 39 wherein said engineering comprises introducing at least one additional copy of the *mon RI* gene as shown in the appended sequence data or a variant thereof.

41. *S. cinnamonensis* containing multiple copies of the *mon RI* gene as shown in the appended sequence data and/or variant(s) thereof.

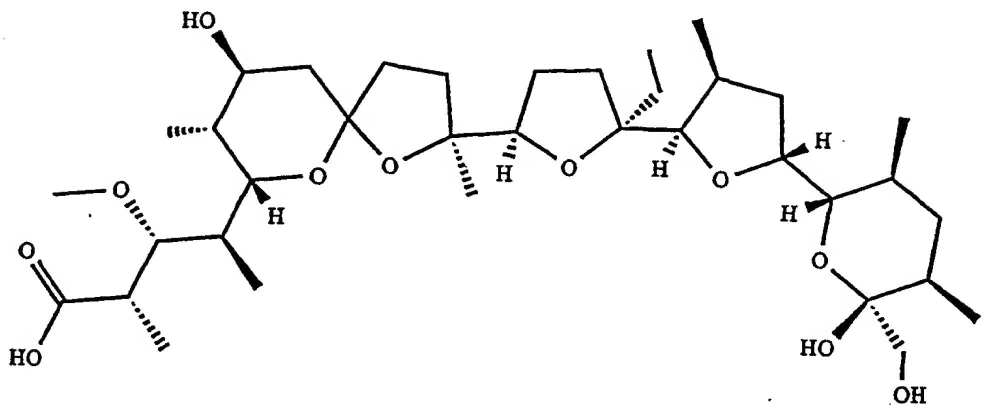
42. A method of producing monensin comprising culturing the organism of claim 41 and/or an organism produced by the method of claim 39 or claim 40.

43. A process for expressing a gene heterologous to *S. cinnamonensis* comprising transforming *S. cinnamonensis* with DNA encoding a heterologous gene and expressing said

gene under control of the activator gene *mon RI* or actII/orf4.

44. A process according to claim 43 wherein said heterologous gene is a PKS gene.

45. 13-Propyl erythromycin A.



monensin A : R = ethyl
monensin B : R = methyl

Fig 1

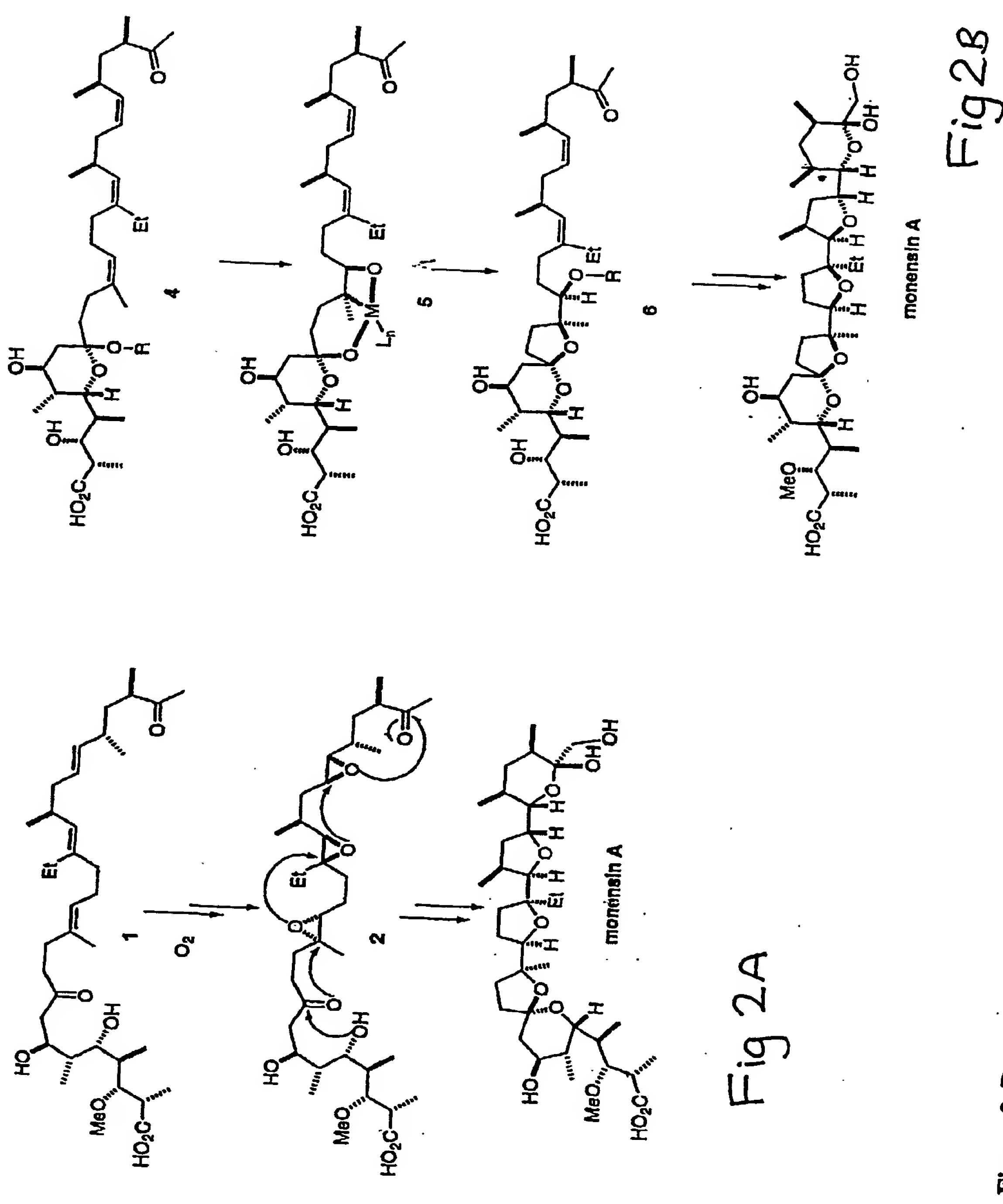


Figure 2. Proposed mechanisms for monensin biosynthesis.

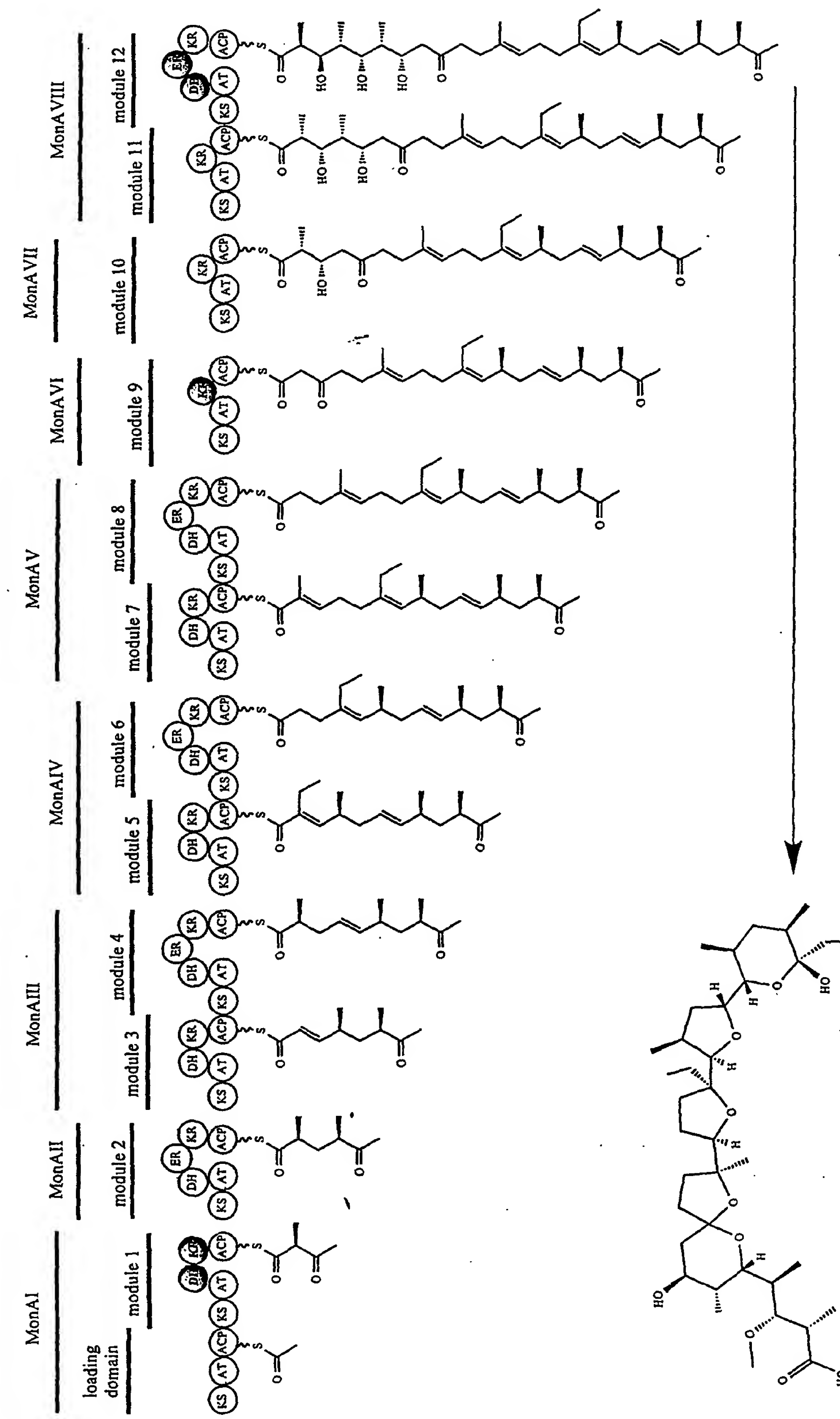


Fig3

Proposed organisation of the monensin PKS

Organisation of the Monensin Biosynthetic Gene Cluster

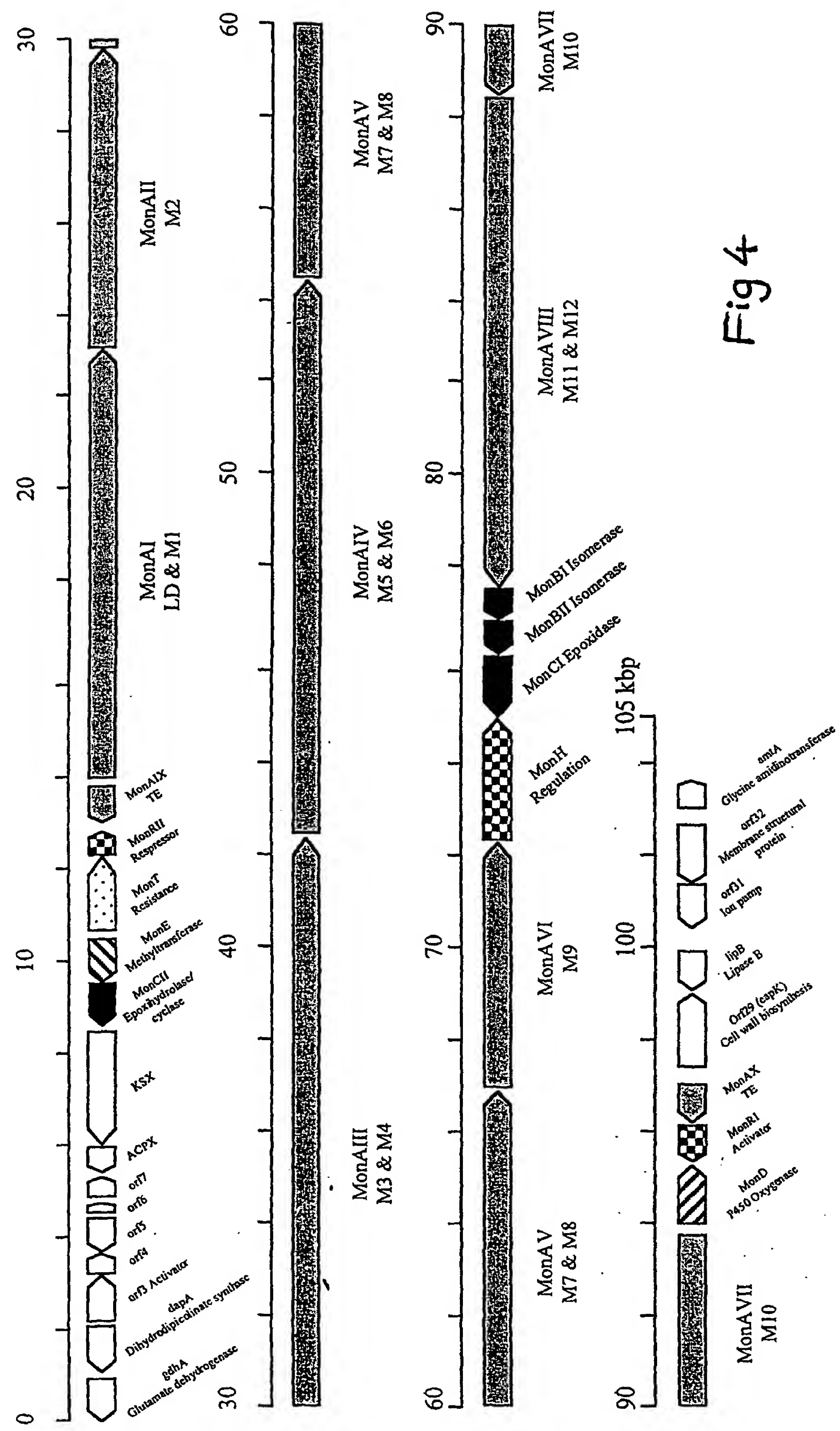


Fig 4

SEQUENCE LISTING

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101 CGGGCCGAGG CGCCGCGGCG CTGGGCGTAG GTGTCCACGC GGGCGCGTTC

151 GACCTCCTTG ACCTGCTTGA GGAGGTCCAG GTCGATGCCC TTCTCGTCGA

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251 GCGAGCTTCT GGATGGTGTA GATGGCGACG TTCCCGGAGC CGGACACGAC

301 CGCCGTCCGG CCTTCGAGGG TCTCGCCGCG CTCACGCAGC ATCGCCGCCG

351 CGAAGAGGAC GTTGCCGTAG CCGGTCGCCT CCGGACGGAT CAGGGAGCCG

401 CCCCAGTTGC GGCCCTTGCC GGTGAGGACG CCCGCCTCCC AGCGGTTGGT

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SUBSTITUTE SHEET (RULE 26)

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SUBSTITUTE SHEET (RULE 26)

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96701 GGTCGGCGAG TTCCCCGATG TCGTCCAGGA GCCGCTCTCT GCGGCGGTCC
96751 TGTCGCCCGG GGTACTGCAC CGCGAGGACC TCGCTGTCGG TCGGGAGAGT
96801 GGGGGATTGC GCAAGGGGGT GGTAGTAGGA GGCCGAGCCG CCCGCGTGGG
96851 GGAAGCAGAC CAGGCGAACG ACGGCTTCCG GTCGGGGCCG GAAGCGACGT
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97301 GGGCCGTTGG CCTGCGCTAT TTGGCAGCCT TCCGTCATGG GTGGTAAAAG
97351 ATCGCCTTTC CCCTCTGGGG TGCCGGTCGA GCTGGCCTCG ACCGCGATTG
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98801 GACGCGGACC ACGTGTGGCA GCGGGCCCAC GACGGGCTGA CCCACCTCCT

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100151 GCGCGAGGGG TCCGTGACCT GGGTGGACGG TCCGGTTGGA CATCCCGGGG

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100551 CCAGCTGGAT CGTCGAGTGG GCCACGTCGA AGTGGCCCCC GACACACCGC

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102651 TACCTGCTCG ATTCCGGGGA GTGCGGTCAC GCCGGGACGA GAGCTCGGTT

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103201 CCCCCGACTG GCAGTCGCGC GGCTTCTGCA ATTCCTGTCC GCGGGACAGC

103251 ATGCTCGTCG TCGGCGACGA GATCATCGAG ACCCCGATGG CGTGGCCGTG

103301 CCGCTGTTTC GAGACGCACT CGTACCGCGA ACTCCTCAAG GACTACTTCC

103351 GGCGCGGCGC GCGCTGGACG GCGGCGCCGC GCCCCCAGCT CACCGAGGCC

103401 CTGTACGAGA AGGACTTCCG CCCTCCCGAG GAGGGCGAAC GATGCGCTAC

103451 ATCCTCACCG AGTTCGAGCC GGTGTTCGAC GCGGCGGATT TCGTGCGGGC

103501 GGGCCGCGAC CTGTTCGTGA CGCGGAGCAA CGTCGCCAAC CTGCTGGGCA

103551 TCGAGTGGCT GCGCCGCCAC CTTCGGGCCG GAGTACCGCG TGCCACGAGA

BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

Professor P.F. Leadlay,
Department of Biochemistry,
University of Cambridge,
80 Tennis Court Road,
Cambridge.
CB2 1GA

NAME AND ADDRESS OF DEPOSITOR

INTERNATIONAL FORM

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT
issued pursuant to Rule 7.1 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified at the bottom of this page

I. IDENTIFICATION OF THE MICROORGANISM

Identification reference given by the DEPOSITOR:

Escherichia coli
XL1-Blue MR (MO-CN11)

Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY:

NCIMB 40956

II. SCIENTIFIC DESCRIPTION AND/OR PROPOSED TAXONOMIC DESIGNATION

The microorganism identified under I above was accompanied by:

☐ a scientific description

☒ a proposed taxonomic designation

(Mark with a cross where applicable)

III. RECEIPT AND ACCEPTANCE

This International Depositary Authority accepts the microorganism identified under I above, which was received by it on 1 July 1998 (date of the original deposit)[1]

IV. RECEIPT OF REQUEST FOR CONVERSION

The microorganism identified under I above was received by this International Depositary Authority on (date of the original deposit) and a request to convert the original deposit to a deposit under the Budapest Treaty was received by it on (date of receipt of request for conversion)

V. INTERNATIONAL DEPOSITARY AUTHORITY

Name: NCIMB Ltd.,

Address: 23 St Machar Drive,
Aberdeen,
AB24 3RY,
Scotland.

Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorised official(s):

Date: 9 July 1998

1 Where Rule 6/4(d) applies, such date is the date on which the status of International Depositary Authority was acquired.

Form BP/4 (sole page)

BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

Professor P.F. Leadlay,
Department of Biochemistry,
University of Cambridge,
80 Tennis Court Road,
Cambridge.
CB2 1GA

NAME AND ADDRESS OF DEPOSITOR

INTERNATIONAL FORM

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT
issued pursuant to Rule 7.1 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified at the bottom of this page

I. IDENTIFICATION OF THE MICROORGANISM

Identification reference given by the DEPOSITOR:	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY:
Escherichia coli XL1-Blue MR (MO-CN33)	NCIMB 40957

II. *SCIENTIFIC DESCRIPTION AND/OR PROPOSED TAXONOMIC DESIGNATION*

The microorganism identified under I above was accompanied by:

☐ a scientific description

☒ a proposed taxonomic designation

(Mark with a cross where applicable)

III. RECEIPT AND ACCEPTANCE

This International Depositary Authority accepts the microorganism identified under I above, which was received by it on 1 July 1998 (date of the original deposit)[1]

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Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorised official(s):

Date: 9 July 1998

1 Where Rule 6/4(d) applies, such date is the date on which the status of International Depositary Authority was acquired.

Form BP/4 (sole page)

BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

Professor P.F. Leadlay,
Department of Biochemistry,
University of Cambridge,
80 Tennis Court Road,
Cambridge.
CB2 1GA

NAME AND ADDRESS OF DEPOSITOR

INTERNATIONAL FORM

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT
issued pursuant to Rule 7.1 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified at the bottom of this page

I. IDENTIFICATION OF THE MICROORGANISM

Identification reference given by the DEPOSITOR:	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY:
Escherichia coli XL1-Blue MR (MO-CN02)	NCIMB 40958

II. SCIENTIFIC DESCRIPTION AND/OR PROPOSED TAXONOMIC DESIGNATION

The microorganism identified under I above was accompanied by:

☐ a scientific description

☒ a proposed taxonomic designation

(Mark with a cross where applicable)

III. RECEIPT AND ACCEPTANCE

This International Depositary Authority accepts the microorganism identified under I above, which was received by it on 1 July 1998 (date of the original deposit)[1]

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1 Where Rule 6/4(d) applies, such date is the date on which the status of International Depositary Authority was acquired.

Form BP/4 (sole page)

BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

Dr. P.F. Leadlay,
Department of Biochemistry,
University of Cambridge,
80 Tennis Court Road,
Cambridge.
CB2 1GA

NAME AND ADDRESS OF THE PARTY TO WHOM THE VIABILITY STATEMENT IS ISSUED

INTERNATIONAL FORM

VIABILITY STATEMENT
issued pursuant to Rule 10.2 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified on the following page

I. DEPOSITOR	II. IDENTIFICATION OF THE MICROORGANISM
Name: AS ABOVE *Address:*	*Accession number given by the* INTERNATIONAL DEPOSITARY AUTHORITY: NCIMB 40956 Date of the deposit or of the transfer[1]: 1 July 1998

III. VIABILITY STATEMENT

The viability of the microorganism identified under II above was tested on 1 July 1998 [2]. On that date, the said microorganism was:

[3]
☒ viable
[3]
☐ no longer viable

1 Indicate the date of the original deposit or, where a new deposit or a transfer has been made, the most recent relevant date (date of the new deposit or date of the transfer).

2 In the cases referred to in Rule 10.2(a)(ii) and (iii), refer to the most recent viability test.

3 Mark with a cross the applicable box.

IV. NDITIONS UNDER WHICH THE VIABILITY TEST HAS BEEN PERFORMED[4]	
V. INTERNATIONAL DEPOSITARY AUTHORITY	
Name: NCIMB Ltd., Address: 23 St Machar Drive, Aberdeen, A24 3RY, Scotland.	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorised official(s): Date: 9 July 1998

4 Fill in if the information has been requested and if the results of the test were negative.

BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

NAME AND ADDRESS OF THE PARTY TO WHOM THE VIABILITY STATEMENT IS ISSUED	
Dr. P.F. Leadlay, Department of Biochemistry, University of Cambridge, 80 Tennis Court Road, Cambridge. CB2 1GA	**INTERNATIONAL FORM** **VIABILITY STATEMENT** **issued pursuant to Rule 10.2 by the** **INTERNATIONAL DEPOSITARY AUTHORITY** **identified on the following page**

I. DEPOSITOR	II. IDENTIFICATION OF THE MICROORGANISM
Name: AS ABOVE Address:	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY: NCIMB 40957 Date of the deposit or of the transfer[1]: 1 July 1998

III. VIABILITY STATEMENT
The viability of the microorganism identified under II above was tested on 1 July 1998 [2]. On that date, the said microorganism was: [3] ☒ viable [3] ☐ no longer viable

1 Indicate the date of the original deposit or, where a new deposit or a transfer has been made, the most recent relevant date (date of the new deposit or date of the transfer).

2 In the cases referred to in Rule 10.2(a)(ii) and (iii), refer to the most recent viability test.

3 Mark with a cross the applicable box.

IV. NDITIONS UNDER WHICH THE VIABILITY TEST HAS BEEN PERFORMED[4]	
V. INTERNATIONAL DEPOSITARY AUTHORITY	
Name: NCIMB Ltd., Address: 23 St Machar Drive, Aberdeen, A24 3RY, Scotland.	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorised official(s): Date: 9 July 1998

4 Fill in if the information has been requested and if the results of the test were negative.

BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

Dr. P.F. Leadlay, Department of Biochemistry, University of Cambridge, 80 Tennis Court Road, Cambridge. CB2 1GA	**INTERNATIONAL FORM** **VIABILITY STATEMENT** **issued pursuant to Rule 10.2 by the** **INTERNATIONAL DEPOSITARY AUTHORITY** **identified on the following page**

NAME AND ADDRESS OF THE PARTY TO WHOM THE VIABILITY STATEMENT IS ISSUED

I. DEPOSITOR	II. IDENTIFICATION OF THE MICROORGANISM
Name: AS ABOVE Address:	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY: NCIMB 40958 Date of the deposit or of the transfer[1]: 1 July 1998

III. VIABILITY STATEMENT
The viability of the microorganism identified under II above was tested on 1 July 1998 [2]. On that date, the said microorganism was: ☒ viable [3] ☐ no longer viable [3]

1 Indicate the date of the original deposit or, where a new deposit or a transfer has been made, the most recent relevant date (date of the new deposit or date of the transfer).

2 In the cases referred to in Rule 10.2(a)(ii) and (iii), refer to the most recent viability test.

3 Mark with a cross the applicable box.

IV. NDITIONS UNDER WHICH THE VIABILITY TEST HAS BEEN PERFORMED[4]

V. INTERNATIONAL DEPOSITARY AUTHORITY	
Name: NCIMB Ltd., Address: 23 St Machar Drive, Aberdeen, A24 3RY, Scotland.	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorised official(s): Date: 9 July 1998

4 Fill in if the information has been requested and if the results of the test were negative.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/02072

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/52 C12N15/76 C12P17/18 C12P19/44 C12P19/62
C12Q1/68 C07H17/08 C07H19/01

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C12P C12Q C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, MEDLINE, STRAND, EMBL, BIOSIS, EMBASE, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DONOVAN M J ET AL.: "Isolation of DNA involved in monensin biosynthesis by Streptomyces cinnamonensis;" ABSTR. ANNU. MEET. AM. SOC. MICROBIOL. 88 MEET., 1988, page 261 XP000949887	1-3,6-14
Y	abstract	30-38

X	ARROWSMITH T J ET AL.: "Characterisation of actI-homologous DNA encoding polyketide synthase genes from the monensin producer Streptomyces cinnamonensis." MOLECULAR AND GENERAL GENETICS, vol. 234, no. 2, August 1992 (1992-08), pages 254-264, XP002149754	1-3,6-14
Y	page 263, right-hand column, line 1-5	30-38

	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 October 2000	08. 01. 2001
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer van de Kamp, M

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MALPARTIDA F ET AL: "Homology between Streptomyces genes coding for synthesis of different polyketides used to clone antibiotic biosynthetic genes" NATURE, vol. 325, no. 6107, 26 February 1987 (1987-02-26), pages 818-821, XP002075972	1-3,6-14
Y	abstract page 819, left-hand column, line 16 -right-hand column, line 1; figure 1 ---	30-38
X	ASHWORTH D M ET AL.: "Selection of a specifically blocked mutant of Streptomyces cinnamonensis: isolation and synthesis of 26-deoxymonensin A." THE JOURNAL OF ANTIBIOTICS, vol. 42, no. 7, July 1989 (1989-07), pages 1088-1099, XP002149776 cited in the application	1-3, 6-14,36
Y	abstract page 1088, line 10-15 scheme 1,2 ---	30-38
X	WO 98 49315 A (KOSAN BIOSCIENCES INC ;UNIV LELAND STANFORD JUNIOR (US)) 5 November 1998 (1998-11-05)	36,45
Y	figure 6G compound #102 example 6 claims 1-10 ---	30-38
X	HOPWOOD D A: "Genetic contributions to understanding polyketide synthases" CHEMICAL REVIEWS, vol. 97, no. 7, November 1997 (1997-11), pages 2465-2497, XP002130647 figures 3,13 table 1 page 2486, paragraph C ---	36
Y	WO 98 01546 A (CORTES JESUS ;LEADLAY PETER F (GB); STAUNTON JAMES (GB); BIOTICA T) 15 January 1998 (1998-01-15) cited in the application page 5, line 12 -page 10, line 11 claims 1-6 ---	30-38

-/--

Intern al Application No
PCT/GB 00/02072

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ZERBE-BURKHARDT K ET AL.: "Cloning, sequencing, expression, and insertional inactivation of the gene for the large subunit of the coenzyme B12-dependent isobutyryl-CoA mutase from Streptomyces cinnamonensis." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 273, no. 11, 13 March 1998 (1998-03-13), pages 6508-6517, XP002149755 abstract ---	
A	ROWE C J ET AL: "Construction of new vectors for high-level expression in actinomycetes" GENE, vol. 216, no. 1, August 1998 (1998-08), pages 215-223, XP004149299 cited in the application abstract ---	
T	WO 00 00500 A (LEADLAY PETER FRANCIS ;CORTES JESUS (GB); STAUNTON JAMES (GB); BIO) 6 January 2000 (2000-01-06) Note: 100.0 % aa seq identity of SEQ ID NO:23 with SEQ ID NO:19 in 920 aa overlap. page 14, line 15-17 page 17, line 15-20 page 24, line 16-20 examples 1,3,26 claim 18 -----	1-3, 6-14, 30-38

International application No.
PCT/GB 00/02072

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

see further information sheet invention 1

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1,8-12,14,43,44 (all partially); 2-7,13,15-42, 45 (all completely)

A DNA sequence comprising the complete monensin (mon) gene cluster, or a part or a variant of it which encodes a polypeptide (or part of it) which is at least 80%, preferably at least 90% identical with one of the peptides according to SEQ ID NOs 12-33 (AcpX to MonAX as set out in table II), provided that said polypeptide is not all or part of amino acid 1-920 encoded by monAI. Vectors, transformed cells, hybridization probes and their uses.

Use of mon genes to control expression (monRI), to effect chain release (monAIX and monAX), to provide a desired stereochemical outcome (monBI and monBII), or to provide epoxidase or cyclase activity (monCI and monCII). Mon polypeptides having isomerase activity (MonBI and MonBII), or having chain terminating activity (MonAIX or MonAX), or having epoxidase activity (MonCI), or having cyclase activity (MonCII).

Processes for producing polyketides involving monensin loading or extension modules or domains. DNA sequences encoding hybrid polyketide synthases containing one or more monensin modules or domains (provided that it is not encoding an ery loading module, the first and second ery extension modules and the ery chain-terminating thioesterase in which the AT domain of the first ery extension module has been substituted by the ethyl malonyl-CoA AT from the monensin synthase), polyketide synthases encoded by said DNA sequences, and polyketide compounds produced by said polyketide synthases. Vectors and transformed cells.

Methods of producing S. cinnamonensis capable of producing enhanced levels of monensin by overexpressing or amplifying the monRI gene, S. cinnamonensis strains produced thereby, and use of said strains in monensin production.

Process for expressing a heterologous gene, e.g., a PKS gene, in S. cinnamonensis under the control of monRI.

2. Claims: 1,8-12,14 (all partially)

A DNA sequence or a part or a variant of it which encodes a polypeptide (or part of it) which is at least 80%, preferably at least 90% identical with a peptide according to SEQ ID NO:5 (GdhA as set out in table II), vectors, transformed cells, hybridization probes and their uses.

3. Claims: 1,8-12,14 (all partially)

A DNA sequence or a part or a variant of it which encodes a polypeptide (or part of it) which is at least 80%, preferably at least 90% identical with a peptide according to SEQ ID NO:6 (DapA as set out in table II), vectors, transformed cells, hybridization probes and their uses.

4. Claims: 1,8-12,14 (all partially)

A DNA sequence or a part or a variant of it which encodes a polypeptide (or part of it) which is at least 80%, preferably at least 90% identical with a peptide according to SEQ ID NO:7 (Orf3 as set out in table II), vectors, transformed cells, hybridization probes and their uses.

5. Claims: 1,8-12,14 (all partially)

A DNA sequence or a part or a variant of it which encodes a polypeptide (or part of it) which is at least 80%, preferably at least 90% identical with a peptide according to SEQ ID NO:8 (Orf4 as set out in table II), vectors, transformed cells, hybridization probes and their uses.

6. Claims: 1,8-12,14 (all partially)

A DNA sequence or a part or a variant of it which encodes a polypeptide (or part of it) which is at least 80%, preferably at least 90% identical with a peptide according to SEQ ID NO:9 (Orf5 as set out in table II), vectors, transformed cells, hybridization probes and their uses.

7. Claims: 1,8-12,14 (all partially)

A DNA sequence or a part or a variant of it which encodes a polypeptide (or part of it) which is at least 80%, preferably at least 90% identical with a peptide according to SEQ ID NO:10 (Orf6 as set out in table II), vectors, transformed cells, hybridization probes and their uses.

8. Claims: 1,8-12,14 (all partially)

A DNA sequence or a part or a variant of it which encodes a polypeptide (or part of it) which is at least 80%, preferably at least 90% identical with a peptide according to SEQ ID NO:11 (Orf7 as set out in table II), vectors, transformed cells, hybridization probes and their uses.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

9. Claims: 1,8-12,14 (all partially)

A DNA sequence or a part or a variant of it which encodes a polypeptide (or part of it) which is at least 80%, preferably at least 90% identical with a peptide according to SEQ ID NO:34 (Orf29 as set out in table II), vectors, transformed cells, hybridization probes and their uses.

10. Claims: 1,8-12,14 (all partially)

A DNA sequence or a part or a variant of it which encodes a polypeptide (or part of it) which is at least 80%, preferably at least 90% identical with a peptide according to SEQ ID NO:35 (LipB as set out in table II), vectors, transformed cells, hybridization probes and their uses.

11. Claims: 1,8-12,14 (all partially)

A DNA sequence or a part or a variant of it which encodes a polypeptide (or part of it) which is at least 80%, preferably at least 90% identical with a peptide according to SEQ ID NO:36 (Orf31 as set out in table II), vectors, transformed cells, hybridization probes and their uses.

12. Claims: 1,8-12,14 (all partially)

A DNA sequence or a part or a variant of it which encodes a polypeptide (or part of it) which is at least 80%, preferably at least 90% identical with a peptide according to SEQ ID NO:37 (Orf32 as set out in table II), vectors, transformed cells, hybridization probes and their uses.

13. Claims: 1,8-12,14 (all partially)

A DNA sequence or a part or a variant of it which encodes a polypeptide (or part of it) which is at least 80%, preferably at least 90% identical with a peptide according to SEQ ID NO:38 (AmtA as set out in table II), vectors, transformed cells, hybridization probes and their uses.

14. Claims: 43,44 (both partially)

Process for expressing a heterologous gene, e.g., a PKS gene, in S. cinnamonensis under the control of actII/orf4.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte[illegible]al Application No
PCT/GB 00/02072

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
WO 9849315	A	05-11-1998	AU	7172298	A	24-11-1998
			EP	0979286	A	16-02-2000
			US	6117659	A	12-09-2000
WO 9801546	A	15-01-1998	AU	3450997	A	02-02-1998
			AU	3451497	A	02-02-1998
			BG	103133	A	28-04-2000
			BR	9710209	A	11-01-2000
			CA	2259420	A	15-01-1998
			CA	2259463	A	15-01-1998
			CN	1229438	A	22-09-1999
			EP	0909327	A	21-04-1999
			EP	0910633	A	28-04-1999
			WO	9801571	A	15-01-1998
			GB	2331518	A	26-05-1999
			NO	990012	A	23-02-1999
			PL	331285	A	05-07-1999
			SK	182498	A	16-05-2000
			AU	7666198	A	30-12-1998
			EP	0983348	A	08-03-2000
			WO	9854308	A	03-12-1998
WO 0000500	A	06-01-2000	AU	4524599	A	17-01-2000
			AU	4524799	A	17-01-2000
			WO	0000618	A	06-01-2000

PATENT COOPERATION TREATY

REC'D 12 JAN 2001
WIPO PCT

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference IS/BP5858469	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/GB 00/02072	International filing date *(day/month/year)* 30/05/2000	(Earliest) Priority Date *(day/month/year)* 28/05/1999
Applicant BIOTICA TECHNOLOGY LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 9 sheets.

[ ] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

 a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

 [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

 b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

 [X] contained in the international application in written form.
 [ ] filed together with the international application in computer readable form.
 [ ] furnished subsequently to this Authority in written form.
 [X] furnished subsequently to this Authority in computer readble form.
 [X] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
 [X] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [X] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

 [X] the text is approved as submitted by the applicant.
 [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

 [ ] the text is approved as submitted by the applicant.
 [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

 [X] as suggested by the applicant.
 [ ] because the applicant failed to suggest a figure.
 [ ] because this figure better characterizes the invention.

 [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 00/02072

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

see further information sheet invention 1

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

ional application No.
PCT/GB 00/02072

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

abstract:
line 8 is modified as follows:
removal of the word 'novel'.

PATENT COOPERATION TREAT

PCT

From the INTERNATIONAL BUREAU

To:
STUART, Ian
Mewburn Ellis
York House
23 Kingsway
London WC2B 6HP
ROYAUME-UNI

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

Date of mailing (day/month/year)
20 September 2001 (20.09.01)

Applicant's or agent's file reference
IS/BP5858469

IMPORTANT NOTICE

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/GB00/02072	30 May 2000 (30.05.00)	28 May 1999 (28.05.99)

Applicant
BIOTICA TECHNOLOGY LIMITED et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   KP,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AG,AL,AM,AP,AT,AU,AZ,BA,BB,BG,BR,BY,CA,CH,CN,CR,CU,CZ,DE,DK,DM,DZ,EA,EE,EP,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,MZ,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,

   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   20 September 2001 (20.09.01) under No. WO 01/68867

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 338.83.38

Record copy

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty

For receiving Office use only

PCT/GB 00 / 02072

International Application No.

30 MAY 2000 30.05.2000

International Filing Date

Name of receiving Office and "PCT International Application" United Kingdom Patent Office PCT International Application

Applicant's or agent's file reference (if desired) (12 characters maximum) IS/BP5858469

Box No. I TITLE OF INVENTION POLYKETIDES AND THEIR SYNTHESIS

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BIOTICA TECHNOLOGY LIMITED
181A HUNTINGDON ROAD
CAMBRIDGE
CB3 0DJ
GB

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

LEADLAY PETER FRANCIS
17 CLARENDON ROAD
CAMBRIDGE
CB2 2BH
GB

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(if this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

STUART, IAN ~~(and others)~~
MEWBURN ELLIS
YORK HOUSE
23 KINGSWAY
LONDON WC2B 6HP
GB

Deleted RO/GB

Telephone No. 0117 9266411

Facsimile No. +44 20 7240 9339

Teleprinter No.

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III **FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS**

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

STAUNTON JAMES
29 PORSON ROAD
CAMBRIDGE
CB2 2ET
GB

This person is:

- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(if this check-box is marked, do not fill in below.)*

State *(that is, country) of nationality:* GB

State *(that is, country) of residence:* GB

This person is applicant for the purposes of:

- [ ] all designated states
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.))*

OLIYNYK MARKO
DEPARTMENT OF BIOCHEMISTRY
CAMBRIDGE UNIVERSITY
TENNIS COURT ROAD
CAMBRIDGE
CB2 1QW
GB

This person is:

- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(if this check-box is marked, do not fill in below.)*

State *(that is, country) of nationality:* UA

State *(that is, country) of residence:* GB

This person is applicant for the purposes of:

- [ ] all designated states
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.))*

This person is:

- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(if this check-box is marked, do not fill in below.)*

State *(that is, country) of nationality:*

State *(that is, country) of residence:*

This person is applicant for the purposes of:

- [ ] all designated states
- [ ] all designated States except the United States of America
- [ ] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.))*

This person is:

- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(if this check-box is marked, do not fill in below.)*

State *(that is, country) of nationality:*

State *(that is, country) of residence:*

This person is applicant for the purposes of:

- [ ] all designated states
- [ ] all designated States except the United States of America
- [ ] the United States of America only
- [ ] the States indicated in the Supplemental Box

- [ ] Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No. V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

- [X] **AP** **ARIPO Patent: GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SL** Sierra Leone, **SZ** Swaziland, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- [X] **EA** **Eurasian Patent: AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- [X] **EP** **European Patent: AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- [X] **OA** **OAPI Patent: BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GW** Guinea-Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* ....

National Patent *(if other kind of protection desired, specify on dotted line)*:

- [X] **AE** United Arab Emirates
- [X] **AL** Albania..........
- [X] **AM** Armenia..........
- [X] **AT** Austria..........
- [X] **AU** Australia..........
- [X] **AZ** Azerbaijan
- [X] **BA** Bosnia & Herzegovina..........
- [X] **BB** Barbados
- [X] **BG** Bulgaria..........
- [X] **BR** Brazil..........
- [X] **BY** Belarus..........
- [X] **CA** Canada
- [X] **CH and LI** Switzerland and Liechtenstein..........
- [X] **CN** China..........
- [X] **CR** Costa Rica
- [X] **CU** Cuba..........
- [X] **CZ** Czech Republic..........
- [X] **DE** Germany..........
- [X] **DK** Denmark..........
- [X] **DM** Dominica
- [X] **EE** Estonia..........
- [X] **ES** Spain..........
- [X] **FI** Finland..........
- [X] **GB** United Kingdom.
- [X] **GD** Grenada
- [X] **GE** Georgia..........
- [X] **GH** Ghana..........
- [X] **GM** Gambia
- [X] **HR** Croatia..........
- [X] **HU** Hungary..........
- [X] **ID** Indonesia
- [X] **IL** Israel..........
- [X] **IN** India
- [X] **IS** Iceland
- [X] **JP** Japan..........
- [X] **KE** Kenya..........
- [X] **KG** Kyrgyzstan..........
- [X] **KP** Democratic People's Republic of Korea..........
- [X] **KR** Republic of Korea..........
- [X] **KZ** Kazakstan..........
- [X] **LC** St Lucia
- [X] **LK** Sri Lanka
- [X] **LR** Liberia.
- [X] **LS** Lesotho..........
- [X] **LT** Lithuania
- [X] **LU** Luxembourg
- [X] **LV** Latvia
- [X] **MA** Morocco
- [X] **MD** Republic of Moldova..........
- [X] **MG** Madagascar..........
- [X] **MK** The former Yugoslav Republic of Macedonia..........
- [X] **MN** Mongolia..........
- [X] **MW** Malawi..........
- [X] **MX** Mexico..........
- [X] **NO** Norway..........
- [X] **NZ** New Zealand..........
- [X] **PL** Poland..........
- [X] **PT** Portugal..........
- [X] **RO** Romania
- [X] **RU** Russian Federation..........
- [X] **SD** Sudan
- [X] **SE** Sweden
- [X] **SG** Singapore
- [X] **SI** Slovenia..........
- [X] **SK** Slovakia..........
- [X] **SL** Sierra Leone
- [X] **TJ** Tajikistan..........
- [X] **TM** Turkmenistan..........
- [X] **TR** Turkey..........
- [X] **TT** Trinidad and Tobago..........
- [X] **TZ** Tanzania
- [X] **UA** Ukraine..........
- [X] **UG** Uganda..........
- [X] **US** United States of America..........
- [X] **UZ** Uzbekistan..........
- [X] **VN** Viet Nam..........
- [X] **YU** Yugoslavia..........
- [X] **ZA** South Africa
- [X] **ZW** Zimbabwe..........

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet:

- [X] **DZ** Algeria
- [X] **AG** Antigua and Barbuda
- [X] **MZ** Mozambique
- [X] ~~Any other state which is party to the PCT~~ ....

Deleted RO/GB

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Supplemental Box ***If the Supplemental Box is not used, this sheet need not be included in the request.***

Use this box in the following cases:

1. If, in any of the Boxes, the space is insufficient to furnish all the information: — ***In such case, write "Continuation of Box No. ..." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient;***

in particular:

(i) if more than two persons are involved as applicants and/or inventors and no "continuation sheet" is available: — *in such case, write "Continuation of Box III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this box is the applicant's state (that is, country) of residence if no state of residence is indicated below;*

(ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: — *in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;*

(iii) if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: — *in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;*

(iv) if, in addition to the agent(s) indicated in Box No. IV, there are further agents: — *in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;*

(v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "Continuation" or "Continuation-in-part": — *in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;*

(vi) if, in Box No. VI, there are more than three earlier applications whose priority is claimed: — *in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.*

(vii) if, in Box No. VI, the earlier application is an ARIPO application: — *in such case, write "Continuation of Box No. VI", specify the number of the item corresponding to that earlier application and indicate at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed.*

2. If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: — ***in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each state so excluded.***

3. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty: — ***in such case, write "Statement Concerning Non-Prejudicial Disclosures or Exceptions to Lack of Novelty" and furnish that statement below.***

Continuation of Box IV

ARMITAGE, IAN M.	PAGET, HUGH C.E.
BRASNETT, ADRIAN H.	SANDERSON, MICHAEL J.
CALDERBANK, T. ROGER	STONER, G. PATRICK
CARTER, STEPHEN	STUART, IAN
COLEIRO, RAYMOND	.WALTON, SEÁN M
CRIPPS, JOANNA E	WATSON, ROBERT J.
FORD, MICHAEL F.	
HACKNEY, NIGEL J.	
HARRISON, DAVID C.	
KIDDLE, SIMON J.	
KREMER, SIMON M.	
LYONS, JUNE, M.	
NICHOLLS, KATHRYN M.	

Continuation of Box No. ?

Sheet No. 5 /GB 00/02072

Box No. VI	PRIORITY CLAIM		☐ Further priority claims are indicated in the Supplemental Box	
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 28/05/99 28 MAY 1999 ▲	9912563.5	GB		
item (2)				
item (3)				

[X] The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s):* (1)

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the supplemental box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

▲ Added
▲▲ Deleted
RO/GB

Choice of International Searching Authority (ISA) *(If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):* ISA /	**Request to use results of earlier search; reference to that search** (if an earlier search has been carried out by or requested from the International Searching Authority): Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following number of sheets		
request	:5	
description (excluding sequence listing part)	:99	
claims	:10	
abstract	:1	
drawings	:4	
sequence listing part of description	~~[74]~~ ▲▲	73 ▲
Total number of sheets	~~[193]~~ ▲▲	192 ▲

This international application is **accompanied by** the item(s) marked below:

1. [ ] fee calculation sheet
2. [ ] separate signed power of attorney
3. [X] copy of general power of attorney; reference number, if any: (x 3)
4. [ ] statement explaining lack of signature
5. [0] priority document(s) *identified in Box No. VI as item(s):*
6. [ ] translation of international application into (language):
7. [X] separate indications concerning deposited microorganisms or other biological matter
8. [ ] nucleotide and/or amino acid sequence listing in computer readable form
9. [X] other *(specify):* 23/77

Figure of the drawings which should accompany the abstract 1

Language of filing of the international application: ENGLISH

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

STUART, IAN
APPOINTED AGENT

For receiving Office use only

1. Date of actual receipt of the purported international application: 30 MAY 2000 30.05.2000	2. Drawings: [✓] received: [ ] not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA/ — 6. [✓] Transmittal of search copy delayed until search fee is paid	

For International Bureau use only

Date of receipt of the record copy by the International Bureau: 21 JUNE 2000 (21.06.00)

RECD 30 AUG 2001
WIPO PCT

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference IS/BP5858469	**FOR FURTHER ACTION** See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB00/02072	International filing date *(day/month/year)* 30/05/2000	Priority date *(day/month/year)* 28/05/1999
International Patent Classification (IPC) or national classification and IPC C12N15/52		
Applicant BIOTICA TECHNOLOGY LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report
   II ☒ Priority
   III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   IV ☒ Lack of unity of invention
   V ☐ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   VI ☒ Certain documents cited
   VII ☐ Certain defects in the international application
   VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
27/12/2000	28.08.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Roscoe, R Telephone No. +49 89 2399 2554

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/02072

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-173 as originally filed

Claims, No.:

1-45 as originally filed

Drawings, sheets:

1/4-4/4 as originally filed

Sequence listing part of the description, pages:

1-80, filed with the letter of 29.09.00

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☐ copy of the earlier application whose priority has been claimed.

   ☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

   Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
   see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☒ the entire international application.

   ☐ claims Nos. .

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1-45 are so unclear that no meaningful opinion could be formed (*specify*):
see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1, 8-12, 14, 43, 44 (all partially).

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1, 8-12, 14, 43, 44 (all partially); 2-7, 13, 15-42, 45 (all completely).

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate she t

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

The documents mentioned in the present International Preliminary Examination Report are numbered as in the search report, i.e. D1 corresponds to the first document of the search report etc.

II. Priority

As the priority document was not available to the IPEA, this opinion / report has been established based upon the assumption that priority was valid. Should this later not turn out to be the case, then D10 may become relevant to the assessment of the present claims.

III. No Opinion

No opinion could be expressed for claims insofar as they relate to unsearched subject-matter (see section IV). Hence, no opinion has been formulated for claims 1, 8-12, 14, 43, 44 (all partially).

Further, the present set of claims as a whole is considered unclear, since the claimed subject-matter is not clearly defined. The reasons for this are set out in section VIII. Hence, no opinion is expressed for any of the present claims.

IV. Lack of Unity

The present application lacks unity and can be divided in to 14 different invention groups as set out in the Annex to the International Search Report. The reasoning for the lack of unity was set out in the invitation to pay additional fees. The International Preliminary Examination Authority agrees with this reasoning. Since applicant failed to pay additional Search Fees, only invention group I can be subject to Preliminary Examination.

Preliminary statement on Novelty, Inventive Step and Industrial Applicability

For the benefit of the applicant, the authorized authority has decided to provide a basic indication of the novelty, inventive step and industrial applicability of

applicants monensin gene cluster. Individual claims will however not be addressed due to the lack of clarity of the claims.

- **Novelty (Art.33(2) PCT)**

None of the cited prior art documents disclose the monensin gene cluster.

- **Inventive Step (Art.33(3) PCT)**

The motivation to isolate the monensin gene cluster is evidenced by prior art attempts using actI probes (e.g. D1 and D2). Data were however inconclusive although complementation data from D1 could be taken to demonstrate partial isolation of the cluster. Further, in view of the conflicting data, D2 (last paragraph) suggests that in the context of the search for monensin, one should test whether eryA-homologous DNA is found in S.cinnamonensis. D6 also suggests that probes based on ery genes should be used for the isolation of modular PKSs (p.2470, col.2). It is indeed the methodology suggested in D2 and D6 which applicant used to isolate the monensin gene cluster. Hence, applicant has merely put the teaching of D2 or D6 into practice. Given the monensin gene cluster, the uses thereof, e.g. for the construction of hybrid PKSs is routine (has been practiced on equivalent PKS enzymes). Hence, the isolation and uses of the monensin gene cluster which have been searched are not considered inventive.

- **Industrial Applicability (Art.33(4) PCT)**

The present claims appear to have industrial applicability.

VI. **Certain documents**

In accordance with Rule 70.10, PCT, applicants attention is drawn to the following document(s):

WO-A-00/00500 (Publication date, 06.01.00; Priority date, 29.06.98; Filing date, 29.06.99)

VIII. Certain observations

- **Clarity (Art.6 PCT)**

The requirement that the claims should be clear does not only apply to individual claims but applies to the claims as a whole. The problems listed below demonstrate how extensive the lack of clarity is in the present claims. Due to this lack of clarity, no examination of the present set of claims can be reasonably carried out.

Claim 1 - "at least part of" - size ?

Claim 2 - "monensin gene cluster" - define by technical features / "variant" - how much variation ?

Claim 3 - "part of" / "allele, mutation or other variant" - define each term

Claim 4 - "at least part" / "monBI,..." - arbitrary definitions, need to be defined by reference to sequences.

Claim 6 - "as set out in the appended sequence data" - show where

Claim 11 - "corresponding polypeptide" - DNA comes from defined in open-ended manner so need to define polypeptide more clearly.

Claim 16 - "binds specifically" - under which conditions ?

Claim 18 - "gene responsible for levels of activity" - definition by result to be achieved. Same applies to subsequent manipulation.

Claims 21-23 - preferences should be defined in dependent claims

Claim 36 - product by process definition. Not acceptable, since combination of known modules of PKSs could arrive at same compounds as can be produced by the broadly defined synthase of claim 35. Major novelty problem.

The above problems are found in numerous claims, yet only the first incidence of the problem has generally been referred to. Claims 1-8, 11, 16, 18-27, 30-32, 34, 36, 39-41 and 43 all contain clarity problems of the types listed above.

PA ı ENT COOPERATION TREAT

From the INTERNATIONAL BUREAU

PCT

COMMUNICATION OF
INTERNATIONAL APPLICATIONS

(PCT Article 20)

Date of mailing:
15 August 2001 (15.08.01)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE
in its capacity as designated Office

The International Bureau transmits herewith copies of the international applications having the following international application numbers and international publication numbers:

International application no.:	International publication no.:
PCT/GB00/02072	

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer:

J. Zahra

Telephone No.: (41-22) 338.83.38

Copy for the elected Office (EO/US)

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

COMMUNICATION IN CASES FOR WHICH NO OTHER FORM IS APPLICABLE

To:

STUART, Ian
Mewburn Ellis
York House
23 Kingsway
London WC2B 6HP
ROYAUME-UNI

Date of mailing (*day/month/year*) 14 August 2001 (14.08.01)	
Applicant's or agent's file reference IS/BP5858469	**REPLY DUE** see paragraph 1 below
International application No. PCT/GB00/02072	International filing date (*day/month/year*) 30 May 2000 (30.05.00)
Applicant BIOTICA TECHNOLOGY LIMITED	

1. ☐ REPLY DUE within ______ months/days from the above date of mailing

   ☐ NO REPLY DUE, however, see below

   ☒ IMPORTANT COMMUNICATION

   ☐ INFORMATION ONLY

2. COMMUNICATION:

The International Bureau regrets to inform the applicant that, due to a clerical error, the above identified international application has not been published promptly after the expiration of 18 months from the priority date, as provided in PCT Article 21(2)(a).

International publication will now take place on 20 September 2001 (20.09.01).

Meanwhile, the International Bureau will communicate a copy of the international application to each designated Office, in accordance with PCT Article 20.

A copy of this notification has been sent to the receiving Office RO/GB and all designated Offices.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 740.14.35	Authorized officer R. Chrem Telephone No. (41-22) 338.83.38

Form PCT/IB/345 (July 1992)

EO/US
PCT/GB00/02072

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing: 20 September 2001 (20.09.01)	
International application No.: PCT/GB00/02072	Applicant's or agent's file reference: IS/BP5858469
International filing date: 30 May 2000 (30.05.00)	Priority date: 28 May 1999 (28.05.99)
Applicant: LEADLAY, Peter, Francis et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International preliminary Examining Authority on:

27 December 2000 (27.12.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was [ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer: J. Zahra Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

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